THE SYNTHESIS OF THE C-RING SUBUNIT OF BRYOSTATIN 1, AND THE SYNTHESIS AND BIOLOGICAL EVALUATION OF FLUORESCENT BRYOSTATIN ANALOGS

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Bryostatin 1 is a complex macrolactone natural product isolated from the marine bryozoan *Bugula neritina*. In recent years, bryostatin 1 has been studied in diseases like cancer, Alzheimer's, stroke, and HIV. The anticancer activity of bryostatin 1 has led to many phase I and phase II clinical trials, and its ability to block the formation of plaques has led to phase II clinical trials for Alzheimer's disease. Bryostatin 1 has been found to be a functional antagonist for protein kinase C mediated responses, and does not exhibit tumor-promoting properties that are associated with phorbol esters.

There is a necessity to produce additional amounts of the marine natural product bryostatin 1 because of it incredibly rich biological profile. One way to address supply issues is through chemical synthesis of bryostatin 1. The first total synthesis of bryostatin 1 was accomplished in 30 longest linear steps and a total of 55 steps. This synthesis involved a highly convergent union of the A-ring and C-ring using the pyran annulation methodology developed by our group. The synthesis of bryostatin 1's C-ring features a olefin/carbonyl metathesis reaction leading to a method to produce fully functionalized C-ring. Bryostatin 7 was also constructed using our synthetic route, and its biological profile was evaluated. Bryostatin 7 differs from bryostatin 1 at the C20 side chain and was found to not be a critical element of bryostatin 1 to obtain the biological responses typical of bryostatin 1.

Constructing simplified bryostatin analogs is another method to address the supply issues of bryostatin 1. Our group has prepared structurally simplified analogs of bryostatin

that rivaled or exceed the activity of bryostatin 1 itself. In 2008, we constructed a structurally simplified bryostatin analog Merle 23 that displayed 'PMA-like' activity in the U937 cell line. We later constructed Merle 28, an analog that resembles bryostatin 1 closely, that displayed 'bryo-like' activity in the U937 cell line. With these results, we hypothesized that the northern half of bryostatin is not simply a spacer domain as suggested in the literature.

In order to understand the underlying mechanism of action of Merle 23 and Merle 28, the design and synthesis of fluorescent analogs were accomplished using a fully functionalized C-ring in our pyran annulation reaction. Incorporation of a fluorescent tag at the C20 position did not have substantial effects on the biological profile (binding affinity for PKC, U937 cells, and Toledo cells). Merle 44 (fluorescent Merle 23) was found to be a functional analog of Merle 23 and Merle 45 (fluorescent Merle 28) was found to be a functional analog of Merle 28.

This dissertation is dedicated
to my parents,
Dr. Joseph Cummins and Vierka Cummins.

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LIST OF ABBREVIATIONS

Δv	geometrical mean of the distances between the 2 outer and the 2 inner signals in an AB spin system (in NMR)
$[\alpha]_D^{20} =$	specific rotation [expressed without units; units, deg mL/(g dm), are understood]
Å	Ångström
Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
BBr_3	boron tribromide
BF_3OEt_2	boron trifluoride etherate
9-BBN	9-borabicyclo(3.3.1)nonane
BINOL	(1,1'-binapthalene)-2,2'-diol
BITIP	catalyst made by combining (1, 1'-binapthalene)-2, 2' diol and $Ti(OiPr)_4$
BOC	*t*-butyl carbonate
BODIPY	4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene
BOM	benzyloxymethyl
BPS	*tert*-butyldiphenylsilyl
Bn	benzyl
Bu	butyl
*n*Bu	butyl

*n*BuLi	*n*-butyl lithium
°C	degrees Celsius
CAA	catalytic asymmetric allylation
calcd	calculated
$CDCl_3$	deuterated chloroform
CDI	carbonyldiimidizole
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
cod	1,5-cyclooctadiene
CSA	10-camphorsulfonic acid
d	day(s); doublet (spectral)
DAG	diacyl glycerol
DEAD	diethyl azodicarboxylate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminun hydride
DIPCl	Chlorodiisopinocampheylborane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethyl sulfide
DMP	2,2-dimethoxypropane

DMSO	dimethyl sulfoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ESI	electron spray impact
DTBMP	2,6-Di-tert-butyl-4-methylpyridine
EtOAc	ethyl acetate
EtOH	ethanol
Et_2O	diethylether
Et_3N	triethylamine
er	enantiomeric ratio
equiv	equivelent(s)
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
GFP	green fluorescent protein
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IC_{50}	50% inhibitory concentration
*i*Pr	isopropyl
Ipc	isopinocampheylborane
im	imidazole

IR	infrared
J	coupling constant (in NMR)
KH	potassium hydride
K_i	binding affinity
LAH	lithium aluminium hydride
LDA	lithium diisopropyl amide
LIDBB	lithium ditertbutylbiphenyl
LLS	longest linear steps
M	moles per liter
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
m	minute(s)
mL	milliliter
MMPP	magnesium monoperoxyphthalate hexahydrate
mol	mole(s)
Mp	melting point
MS	molecular sieves
$NaBH_4$	sodium borohydride

NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
Na_2SO_4	sodium sulfate
NH_4Cl	ammonium chloride
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o-tol	2-methylphenyl
ORTEP	oak ridge thermal ellipsoid plot
PCC	pyridinium chlorochromate
Ph	phenyl
PKC	protein kinase C
PMA	phorbol-12-myristate-13-acetate
PMB	*p*-methoxybenzyl
ppm	parts per million (in NMR)
PPTS	pyridinium *p*-toluenesulfonate
*i*Pr	isopropyl
Py	pyridine
prenyl	3-methyl-2-buten-1-yl
q	quartet (spectral)
RCM	ring-closing metathesis
Rb	round bottom

R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (NMR); second(s)
SAR	structure activity relationship
$SO_3 \cdot Pyr$	sulfur trioxide pyridine complex
t	triplet (spectra)
TBAF	tetrabutylammonium fluoride
*t*Bu	tertiary butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	Trifluoromethanesulfonoyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N,N*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl, tetramethylsilane
TNFα	tumor necrosis factor alpha
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl
Ts	4-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

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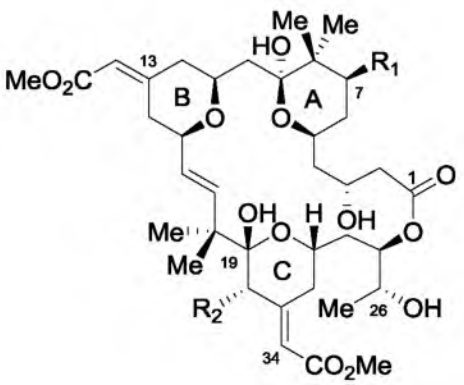
CHAPTER 1

THE SYNTHESIS OF THE C-RING SUBUNIT OF BRYOSTATIN 1; THE BIOLOGICAL EVALUATION OF BRYOSTATIN 7

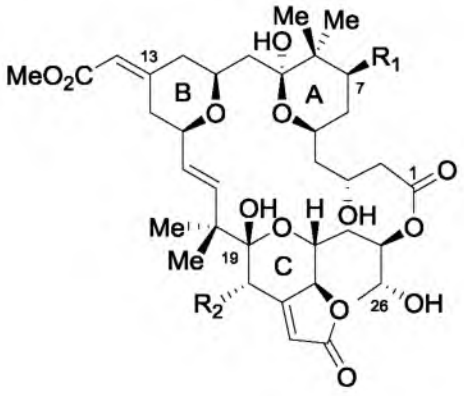
Introduction

In the late 1950s the National Cancer Institute (NCI) instituted a comprehensive program designed to identify new anticancer leads from the extracts of animals, plants, and microorganisms. In the 1960s, Pettit and coworkers discovered that the extracts from the marine bryozoans *Bugula neritina*, found in the Gulf of Mexico, had anticancer properties towards murine P388 lymphocytic leukemia cells.[1] After isolation, one of the active agents in the extracts was identified as bryostatin 1. The structure of bryostatin 1 was elucidated through a combination of analytical techniques that included ^{1}H and ^{13}C NMR, high resolution mass spectroscopy, and X-ray crystallography.[2] Since the structural elucidation of bryostatin 1, 19 other bryostatins have been isolated (Figure **1.1**).[3]

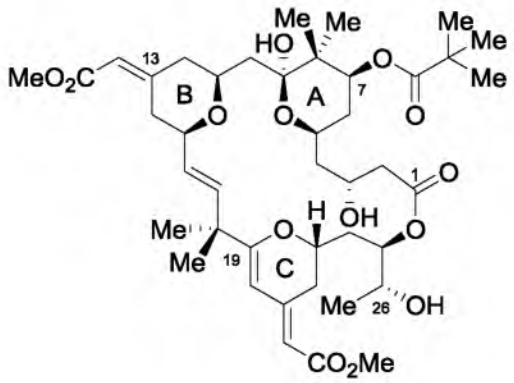
The bryostatins consist of a 20 membered macrocyclic lactone with 3 embedded highly functionalized pyran rings that are referred to as the A-ring, B-ring, and C-ring. The B-ring and C-ring both contain an α,β-unsaturated methyl ester at the 4 position of the pyran and are connected by a *trans* olefin adjacent to a *gem*-dimethyl group. The structure of bryostatin has a network of hydrogen bonds. There is a bifurcated hydrogen bond between the C3 hydroxyl proton and the A and B pyran oxygens, and a second structure of bryostatin has a network of hydrogen bonds. There is a bifurcated hydrogen bond



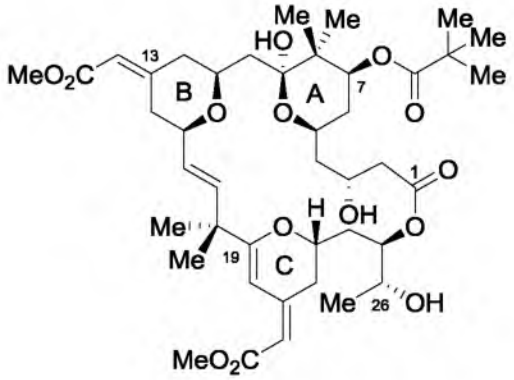
bryostatin	R_1	R_2
1	OAc	$OCO(CH=CH)_2Pr$
2	OH	$OCO(CH=CH)_2Pr$
4	OCO*t*Bu	OCOPr
5	OCO*t*Bu	OAc
6	OCOPr	OAc
7	OAc	OAc
8	OCOPr	OCOPr
9	OAc	OCOPr
10	OCO*t*Bu	H
11	OAc	H
12	OCOPr	$OCO(CH=CH)_2Pr$
13	$OCO(CH)_4Pr$	H
14	OCO*t*Bu	OH
15	OAc	$OCO(CH=CH)_2CH(OH)Et$



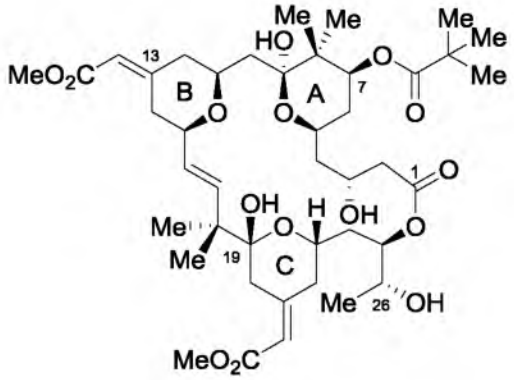
bryostatin	R_1	R_2
3	OAc	$OCO(CH=CH)_2Pr$
19	OCO*t*Bu	OCOPr
20	OCO*t*Bu	H



bryostatin 16



bryostatin 17



bryostatin 18

Figure 1.1 The Bryostatin Family of Natural Products

bond between the C3 hydroxyl proton and the A and B pyran oxygens, and a second hydrogen bond between the C3 oxygen and the C19 hydroxyl proton. Most of the differences between the bryostatins occur at the C20 and C7 positions where they have different combinations of ester groups and hydroxyl groups. Bryostatin 3, 16, 17, 18, and 20 also contain additional structural differences on the C-ring portion of the molecule. While *Bugula neritina* was originally thought to produce the bryostatins, more recent literature suggest that a symbiotic bacteria actually produces the natural product.

Candidus endobugula sertula is the symbiotic bacterium that is believed to be responsible for producing the bryostatins.[4] It is suggested that the bacteria produce these natural products to protect the bryozoan from predation and in return receive an environment in which to grow.[5] Further studies have shown that eliminating the symbiotic bacteria *E. sertula* with the use of the antibiotic gentamicin resulted in a 98% reduction of bryostatins produced by the organism.[6] The number of *B. neritina* colonies in nature producing detectable amounts of bryostatins was found to be very low. The amounts varied from different colonies, time of the year, depth, and geographic locations.[7] Generally, isolation yields tend to range between 10^{-3} to 10^{-8} %.[3] The largest isolation of a bryostatin was in 1991 where 18 g of bryostatin 1 was isolated from 10,000 gallons of wet *B. neritina*.[8] This large scale isolation was done in anticipation of many biological studies which included formulation studies, preclinical toxicology, and clinical trials in cancer patients. Since then, other viable means to obtain additional amounts of bryostatins have been investigated. This is due to potential environmental impact on *B. neritina* and other organisms that depend on its existence.

Aquaculture of *B. neritina* has been investigated as a way of producing more

bryostatin 1.[9] Unfortunately the company investigating this, CalBioMarine Technologies, dissolved in May of 2004. More promising results have been found by the Haygood group and they have identified the *bryA* gene cluster.[10] The Haygood group is exploring the possibility of expressing these genes in a suitable host, resulting in the production of bryostatin 0. Bryostatin 0 is a hypothetical compound that differs from bryostatin 1 at the C7, the C14, and the C20 positions. From this intermediate, it might be possible to obtain bryostatin natural products through synthetic manipulations.

The Biological Activity of Bryostatin 1

The life extension assays in the murine leukemia cell line in mice demonstrated that the bryostatins were a collection of potent oncolytic agents (Table **1.1**).[11] During the initial biological evaluation of the bryostatins, it was realized that their response to P388, L1210, and KB cells mimicked the response shown by the extracts from euphorbiaceae and thymelaeaceae. These plants contain phorbol esters and since they are known PKC activators, it was hypothesized that the bryostatin natural products might be too. This was shown to be true in a study by Pettit and Blumberg in which binding affinity was measured by competitive binding assays using a mixture of PKC isozymes (Table **1.1**).[12] The binding affinity of bryostatins 1-11, which differ only at the C7 and C20 positions, revealed only a moderate change in affinity. Bryostatin 16 and 17 had 100 fold less binding affinity due to their simplified C-ring. Despite the immense interest in bryostatin 1, there is very little known about the biological profiles of the other bryostatins. This is most likely due to the scarcity of material for biological testing.

Table 1.1. *In vitro* ED50 and Murine *in vivo* Life Extensions in P388 Leukemia Cells

bryostatin	ED_{50} (ng/mL)	Life Extension(dose: mg/kg)	K_i for PKC (nM) (mixture of isozymes)
1	0.23	52-96% (10-70)	1.35
2		60% (30)	5.86
3		63% (30)	2.75
4	0.1-1.0	62% (46)	1.30
5	0.26-1.3	88% (185)	1.04
6	0.01	82% (185)	1.18
7	0.026	77% (92)	0.84
8		74% (110)	1.72
9	1.2	40% (80)	1.31
10	0.26	34% (10)	1.56
11	0.018	64% (92.5)	4.82
12	14	47-68% (30-50)	
13	5.4		
14	330		
15	1400		
16	9.3		118
17	19		188
18	3.3		4.82

Bryostatin 1 and Cancer

Much of the literature suggests that PKC plays a key role in cancer. Bryostatin 1 exerts its tumor suppressive ability by inhibiting cell growth, not by cytotoxic effects.[13] Bryostatin 1 was originally isolated for its ability to inhibit the growth of murine P388 lymphocytic leukemia, but has since been found to be effective in other types of leukemia cells (Table **1.2**).[13-14] Additionally, bryostatin 1 demonstrates activity in human A549 lung carcinoma, murine 4T1 p53 null mammary, murine L10A B lymphoma, murine M5076 reticulum carcinoma, and murine B16 melanoma cell lines.[15] *In vivo* assays demonstrated that mice with P388 lymphocytic leukemia doubled their life expectancy when treated with bryostatin 1. It also cured mice with M5 ovary carcinoma and B16 melanoma.[16]

Table 1.2. Bryostatin 1 in Human Leukemia Cell Lines

Cell Line	IC_{50} (nM)
REH (Leukemia)	0.01-0.1
K562 (Leukemia)	0.1-1
CMMol (Leukemia)	0.1-10
HL-60 (Leukemia)	1
CCRF-CEM (Leukemia)	1-10
KG-1 (Leukemia)	1-10
MOLT-4 (Leukemia)	100-1000

In 1993, bryostatin 1 entered its first clinical trial as a single agent for cancer. It was used in a variety of phase I and II clinical trials in patients with carcinomas such as solid tumors (melanoma, renal, and ovarian) and leukemia.[17] In these studies there were no consistent results observed in the patient populations and severe myalgia was dose limiting. Unfortunately, bryostatin 1 did not show promise as a single therapeutic reagent for cancer for these reasons, but has recently shown potential when combined with established anticancer agents.

In contrast to many oncolytic agents, bryostatin 1 stimulates the immune system. This is particularly impressive since anticancer agents target rapidly dividing cells, and thus often impact the immune system. Bryostatin 1 stimulated the production of inflammatory cytokines IL-1β, IL-6, Il-8 and tumor necrosis factor α (TNF- α).[18] It also has been shown to activate T-cells and neutrophils.[19] This remarkable activity has promoted research in immunotherapy, which uses the immune system to target and eliminate cancer cells. Drugs which have been used in combination with bryostatin 1 include vincristine, paclitaxel, cisplatin, fluarabine, temsirolimus, and gemcitabine.[17] Even through the responses in carcinomas were initially reported to be promising there is only a

handful of current clinical trials using bryostatin 1 synergistically with other drugs. Whether or not additional trials will be conducted is largely unknown.

Bryostatin 1 and Neurodegenerative Diseases

In recent years, bryostatin 1 has shown promise in the treatment of CNS disorders such as stroke and Alzheimer's disease (AD). It has shown remarkable results in animal models by inducing new synaptic growth, rescuing dying neurons, and normalizing of amyloid plaques. For example, treatment with bryostatin 1 resulted in curative neurogenesis, synaptogenesis, and cognitive improvement in mice with ischemia/hypoxia induced stroke.[20] Bryostatin 1 has also been shown to reduce the formation of amyloid plaques in transgenic mice by activating the secretion of α-secretase via PKCε.[21] In 2009, the FDA approved the use of bryostatin 1 in phase II clinical trials in the treatment of AD based on preclinical results. The Banchette Rockefeller Neurosciences Institute is the main institution studying bryostatin 1 as a therapy of AD under the guidance of Dr. Daniel Alkon and the results from these clinical trials have not been released as of today.

Bryostatin 1 and Human Immunodeficiency Virus (HIV)

One of the major problems in treating HIV with the standard treatments is that it does not address the latent form of the virus. These HIV latent reservoirs are located in T-cells and monocyte/macrophages, and remain latent until its transcription factors are unregulated.[22] Noncarcinogenic PKC activators, like bryostatin 1, have been shown to reactivate latent HIV-1 by the PKC or ampK pathways, making them interesting therapeutic agents in the treatment of HIV.[23] Bryostatin 1 seems to be ready for clinical

trials for the treatment of HIV but have been hampered by a limited supply. There has been a tremendous effort to produce additional synthetic bryostatin 1 or biologically equivalent simplified analogs. Bryostatin 1's biological responses are linked to the observed binding affinity to the C1 domain of PKC (K_i for PKC, 1.35 nM). Understanding the complex relationship between PKC and bryostatin 1 is vital to understanding how to mimic its biological profile.

Structure and Function of Protein Kinase C (PKC)

The dysfunction of the cellular pathways associated with protein kinase C has been linked to illnesses like cancer[24] and neurological diseases[25], making it an exciting therapeutic target. PKCs are enzymes that catalyze the phosphorylation of the amino acids serine and threonine. They are involved in many critical events such as intracellular signal transduction cascades, apoptosis, cell differentiation, and proliferation.[26]

PKCs consist of 2 major domains, the C-terminal catalytic domain and the N-terminal regulatory domain (Figure **1.2**).[27] The catalytic domain contains the ATP binding site, and is largely conserved amongst protein kinases. Small molecules inhibiting the catalytic domain, like ruboxistaurin[28] and enzastaurin[29] have been identified as PKCβ isozyme selective inhibitors but did not make it past phase III clinical trials.[30] The regulatory domain contains the pseudosubstrate, C2, and C1 segments. PKC can be modulated at the regulatory domain by endogenous 1,2-diacylglycerols (DAGs) and other small molecules like bryostatin 1 and phorbol esters that bind to the C1 domain.

The PKC family is divided into 3 categories according to the structure of the regulatory domain and cofactor requirements (Figure **1.2**).[27, 31] There are at least ten unique

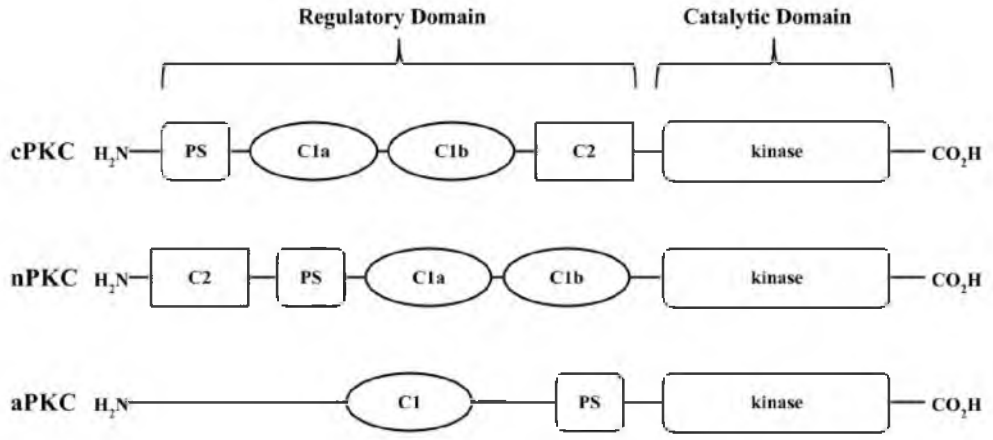


Figure 1.2. Schematic Representation of PKC Family

mammalian isozymes which are grouped into classical (cPKC), novel (nPKC), and atypical (aPKC) PKCs. The distribution of these subtypes varies among different tissues and cell types. All the isozymes are dependent on anionic phospholipids (Ptd-L-Ser) for activation. The cPKC isozymes (α, βI, βII, γ) require both calcium and an endogenous a DAG ligand; nPKC isozymes (ε, δ, η) only require DAG, whereas aPKC isozymes (ζ, τ) do not require calcium or DAG.

PKCs are allosterically regulated by their pseudosubstrate.[32] In PKCs inactive form, the pseudosubstrate is bound to the catalytic domain and the C1b region blocks the ATP binding site, rendering the enzyme inactive.[33] In order to be activated cPKC and nPKC, they must bind to endogenous DAGs. The primary mechanism of DAG is to interact with the C1 domain of PKC.[34] The inactive form of PKC binds to DAG in the cytosol, resulting in a conformational change in the enzyme, removing the pseudosubstrate from the ATP-binding site. The activated PKC then translocates to the cell membrane where it finds ATP and various cofactors.[33] Once fully initiated, PKC then phosphorylates specific protein

substrates, giving its biological activity. PKCs active form is vulnerable to cleavage at the hinge region by calpain and caspase.[35] The result can either be down regulation of PKC through its breakdown or induction of other activities caused by the liberated catalytic and regulatory domains.[34]

Tumor-Promoting Natural Products that Target the C1 Domain

Phorbol-12-myristate-13-acetate (PMA) represents the most studied member of the phorbol ester family (Figure **1.3**). It was originally isolated from the shrub *Croton tiglium*.[36] PMA was found to be a potent tumor-promoter of mouse skin carcinogenesis and was later found to target the C1 domain of PKC (K_i= 0.55 nM).[37] A crystal structure of the C1b domain of PKCβII with PMA has been reported.[38] Its function as a tumor-promoter is currently being evaluated as a differentiation agent where it forces cancer cells into maturation in use with other therapeutic agents.[39]

The aplysiatoxins are a family of spiroketals that were isolated from the sea hare *Stylocheilus longicauda* (Figure **1.3**).[40] Aplysiatoxin has a measured K_i value of 3.0 nM for PKCδ, but it is a tumor-promoter.[41] Indolactams are another PKC C1 domain ligand that was isolated from *Streptomyces mediocicus*.[42] Similarly to phorbol esters, indolactams are thought to interact with PKC through hydrogen bonds using the C11 amide and C14 alcohol.[43] Indolactam V is the simplest of the family and shows a K_i value of 80 nM. Like Aplysiatoxin, it too is a tumor-promoter.[44]

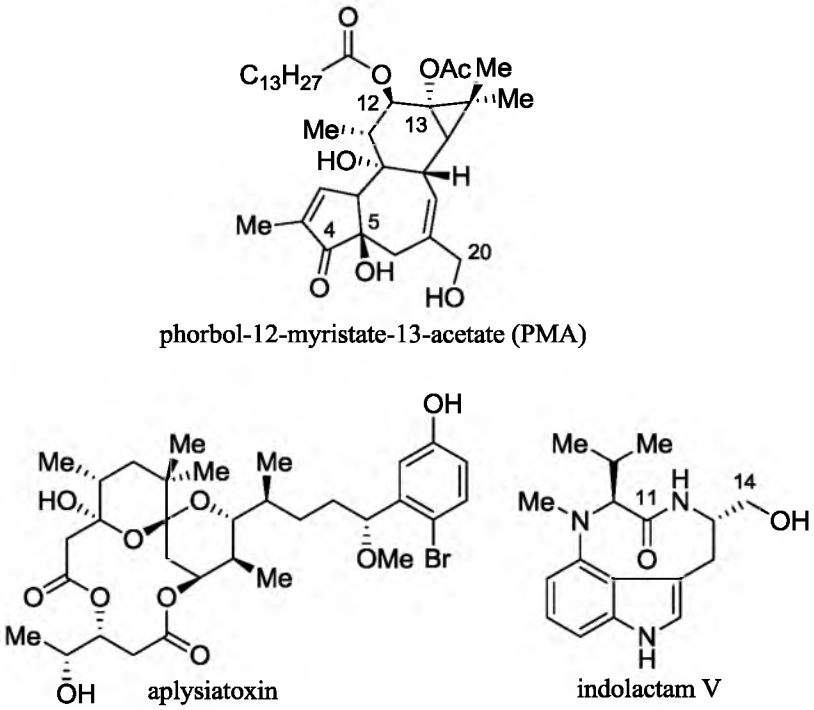


Figure 1.3. The Structures of Tumor-Promoting PKC Ligands

Nontumor-Promoting Natural Products that Target the C1 Domain

Several natural products are currently in or are approaching clinical trials (Figure **1.4**). 12-deoxy-phorbol 13-aceate (prostatin) was first isolated from the plant *Homalanthus nutans*.[45] This compound was found to have an identical skeletal backbone to the phorbol esters but lacked the C12 hydroxyl/acyl group. Like phorbol esters, prostatin binds to PKC and show a K_i value of 12.5 nM for PKC. They show a modest decrease in affinity when compared to PMA. The deletion of the C20 group also changes the biological activity. This small difference in structure makes this ligand nontumor-promoting and has been suggested to be an effective therapy to address latent HIV.[46]

The ingenols are another class of natural products that are closely related to phorbol esters and prostatins. The most studied ingenol is PEP005, which was isolated from

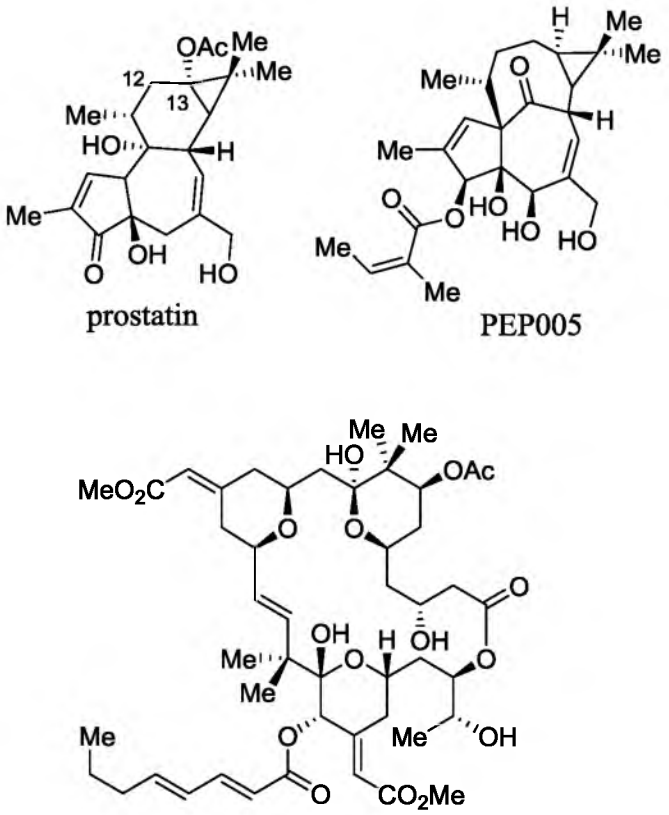


Figure 1.4. The Structures of Nontumor Promoting PKC Ligands

Euphorbia peplus L.[47] PEP005 has a very high binding affinity to PKC, 0.1-0.4 nM depending on the isozyme.[48] PEP005 is another example of a nontumor-promoting PKC activator that was FDA approved for the treatment of actinic keratosis in 2012. Bryostatin 1 is another natural product that binds to the C1 domain with high affinity and does not demonstrate tumor-promoting activity. A need for additional amounts of the bryostatins for biological testing has led to extensive research in the area of total synthesis.

Previous Total Syntheses of the Bryostatins

The bryostatins have been immensely important targets for the last 30 years in the area of natural product synthesis. Their rarity coupled with remarkable biological activity has led to intense research to construct these molecules, with each researcher tackling unique challenges in constructing their skeletons. The first synthesis of a bryostatin was the synthesis of bryostatin 7 by the Masamune group in 1990.[49] Since then, Evans[50], Yamamura[51], Trost [52], Keck[53], Wender[54], and Krische[55] have produced their own synthesis of different bryostatins. The general strategy to construct these complex natural products and how the southern portions of these molecules were constructed is evaluated in the following segments.

Masamune's Total Synthesis of Bryostatin 7[49]

In 1990, the Masamune group reported the first synthesis of bryostatin 7 which was the first synthesis of any bryostatin. The synthetic strategy involved the union of 2 very complex pieces: the A-B portion and functionalized C-ring (Figure **1.5**). The key disconnection in this synthesis was the C16-C17 double bond, which was envisioned to be constructed through a Julia olefination reaction and a macrolactonization of the *seco* acid. The C-ring pyran **1.2** was envisioned to be constructed through a cyclization of the corresponding keto alcohol **1.1**. The intermediate **1.3** would be divided into 2 portions and put together through an organometallic addition of iodide **1.5** into the C20 aldehyde **1.4**.

Masamune's synthesis of bryostatin 7 has been heavily reviewed, so an abbreviated scheme for the construction of sulfone **1.2** is shown in Figure **1.6**. Aldehyde **1.4** started from commercially available 2,2-dimethylpropane-1,3-diol and was made in 15 steps.

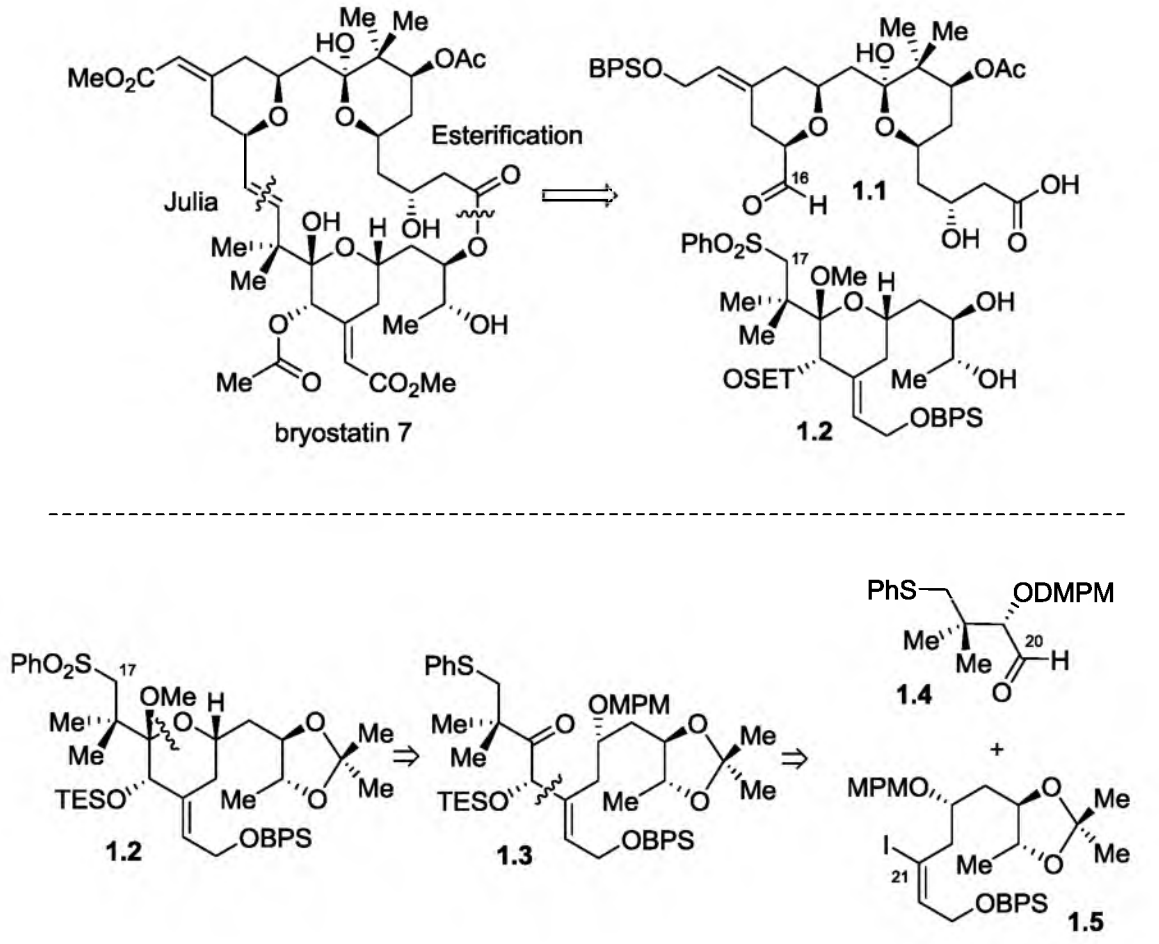


Figure 1.5. Masamune's Retrosynthesis of Bryosatin 7

Vinyl iodide **1.5** was constructed from L-threonine in 14 steps. Lithium halogen exchange of the vinyl iodide, followed by a chelation controlled addition into aldehyde **1.4** produced alcohol **1.7** as a 6:1 dr. The C20 alcohol **1.7** was protected as the TES ether, the DMPM ether was removed, and C19 alcohol was oxidized using Albright-Goldman conditions to give ketone **1.8**. The phenyl sulfide was oxidized to the sulfone and the PMB ether was removed using DDQ producing a hemiketal intermediate. Methyl ketal formation was accomplished using TESOTf/TMSOMe and completed the synthesis of sulfone **1.2**. The C17-C27 segment was constructed in 36 total steps (22 longest linear).

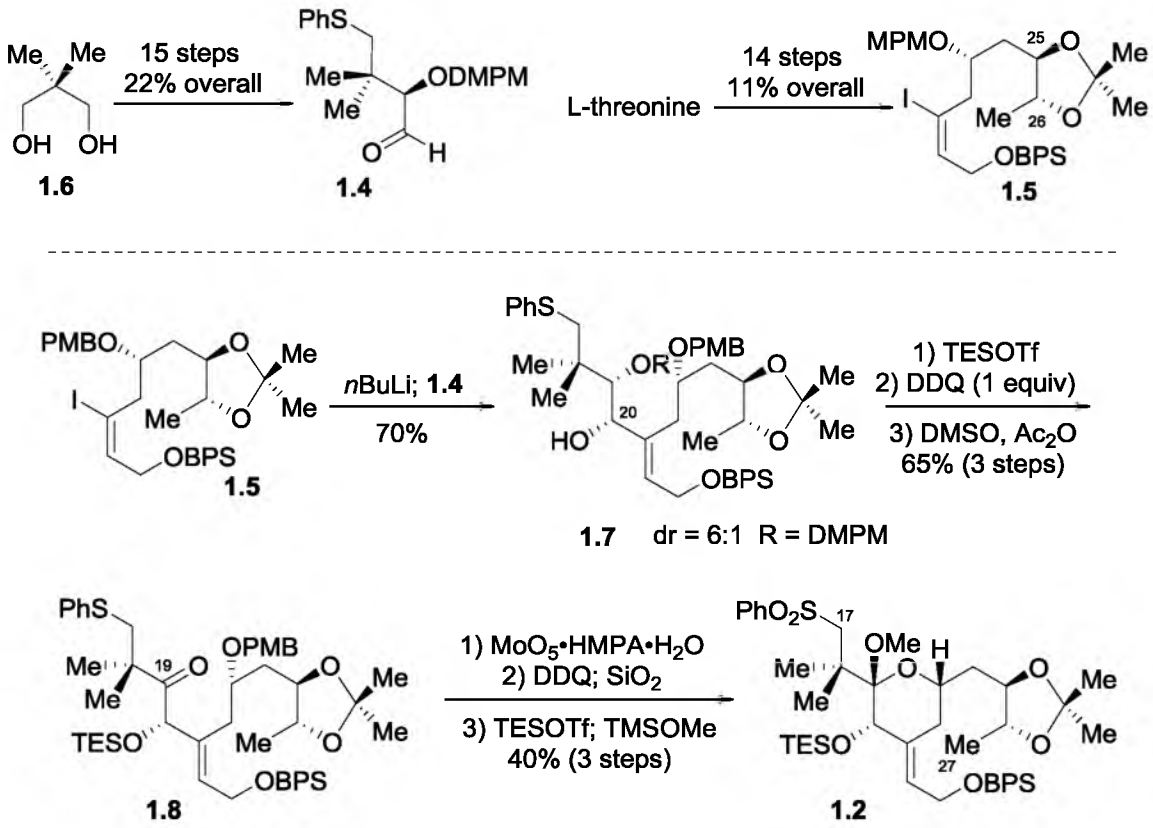


Figure 1.6. Synthesis of C-ring Sulfone

Evans' Total Synthesis of Bryostatin 2[50]

The Evans group completed the first total synthesis of bryostatin 2 in 1999. The retrosynthetic plan involved dividing the molecule into 3 almost equally complex pieces. Like Masamune's synthesis, the B-ring and C-ring would be joined through a Julia olefination reaction installing the C16-C17 *trans* double bond (Figure **1.7**). The A-ring and B-ring would be connected through a displacement reaction of the triflate, shown in Figure **1.8**. The A-ring and C-ring would be connected at the O25 and C1 lactone bond, leading to the macrolactone. Dividing bryostatin 2 into 3 parts gives flexibility when coupling the rings together, but in the end B+C→BC+A→ABC was found to be the best sequence for coupling these pieces.

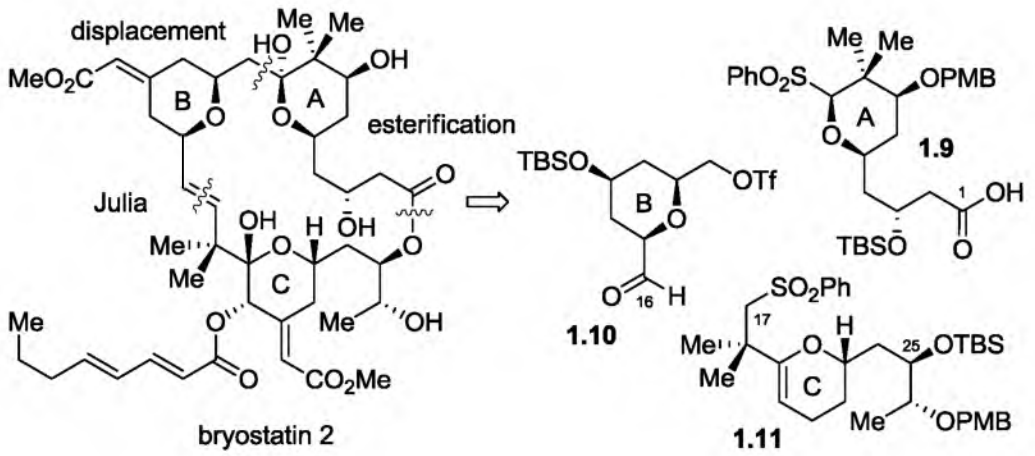


Figure 1.7. Evans' Retrosynthesis of Bryostatin 2

The construction of the C-ring of bryostatin 2 is shown in Figure **1.8**. Commercially available 2,2-dimethyl-1,3-propanediol was monotosylated, displaced by phenyl sulfide, and then oxidized to give the sulfone intermediate. The alcohol was oxidized to the aldehyde **1.12**, which was reacted with the Grignard reagent derived from 5-bromo-1-pentene. Oxidation of the resulting alcohol, followed by oxidative cleavage of the terminal alkene provided keto aldehyde **1.13**. An aldol reaction between aldehyde **1.13** and ketone **1.14** was successfully accomplished through a (-)-DIPCl (Ipc_2BCl or Chlorodiisopinocamphenylborane) mediated double stereo differentiation, resulting in the β-hydroxy ketone **1.15** with a 13:3 dr. The C25 ketone was reduced using Evans-Tishchenko conditions, giving the diol monoester **1.16** as a single diastereoisomer. The C20 alcohol in **1.16** was protected as the TBS ether followed by hydrolysis of the C23 nitrobenzoate ester with LiOH. Hydroxyketone **1.17** was cyclized under acidic conditions resulting in the formation of glycal **1.11**. Unfortunately, installing the C19, C20 and C21 functionality proved to be incompatible with the Julia olefination reaction. The C17-C27 segment was constructed in 13 longest linear steps (LLS) and a total of 16 steps.

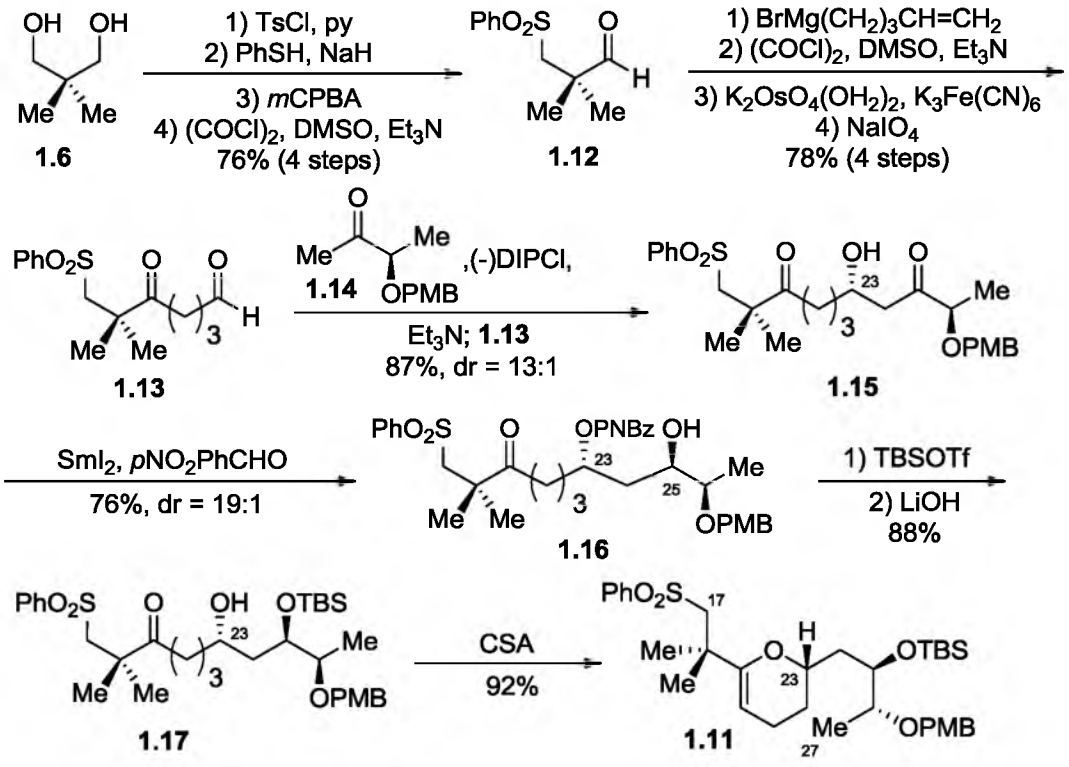


Figure 1.8. Synthesis of the C-ring Glycal **1.11**

Yamamura's Total Synthesis of Bryostatin 3[51]

Bryostatin 3 is the most complex member of its family due to an additional stereocenter at the C22 inside the pryan-butenolide structure (Figure **1.9**). Its total synthesis was accomplished by the Yamamura group in 2000. Similarly to the 2 previous syntheses, a Julia reaction was planned to connect the B-ring and C-ring. This reaction would result in the formation of the C16-C17 *trans* olefin and an esterification reaction would complete the 20-membered macrolactone. The C-ring was envisioned to be constructed through an acid catalyzed cyclization of the corresponding keto alcohol **1.21**. This intermediate would come from 2 separate portions that would be coupled through an addition of iodide **1.23** into α-alkoxy aldehyde **1.22** to give the C22 stereocenter.

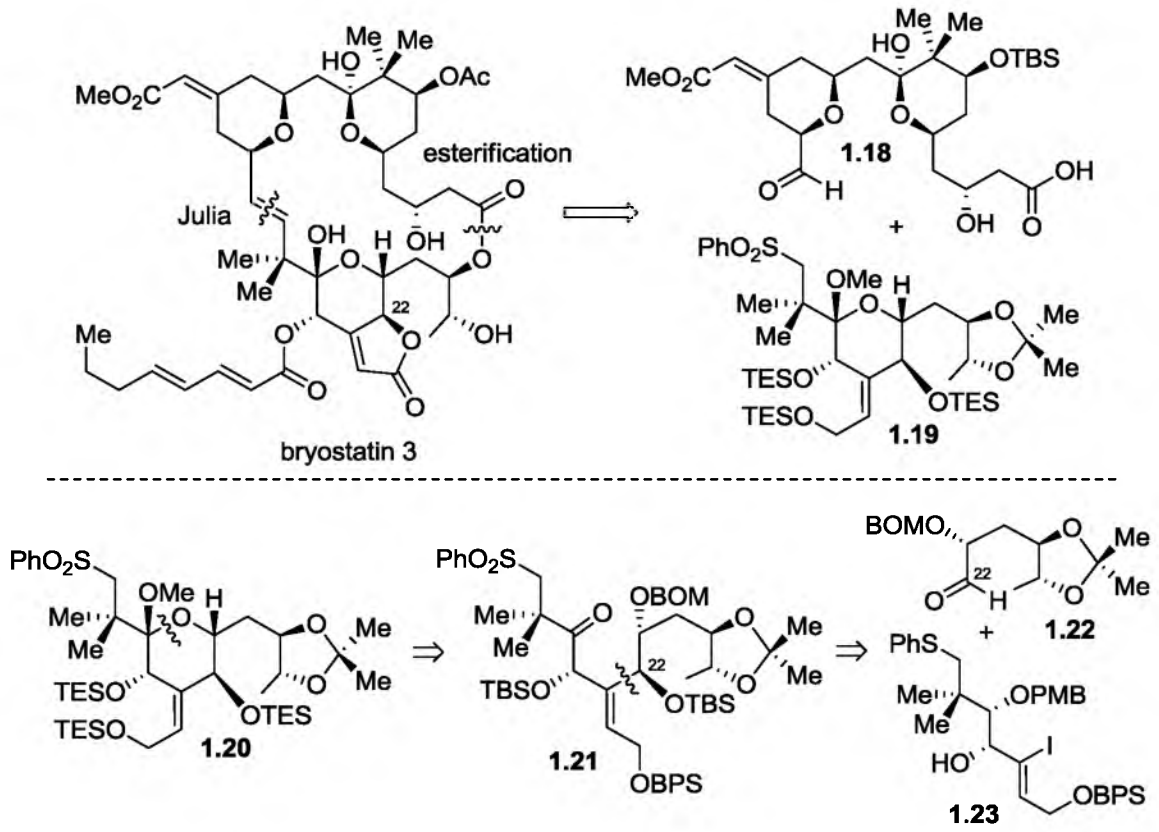


Figure 1.9. Yamamura's Retrosynthesis of Bryostatin 3

A summarized scheme of Yamamura's construction of the C17- C27 subunit is shown in Figure **1.10**. The C-ring is divided into 2 major portions. The left half of the molecule **1.23** was made in 16 steps from 2-dimethylpropane-1,3-diol and the right half **1.22** was made from glucose in 11 steps. The union between the 2 pieces was accomplished using lithium halogen exchange on **1.23** and reaction with aldehyde **1.22**, affording a 3:1 mixture of diastereomers. The C20 and C22 alcohols were protected as TBS ethers, the sulfide was oxidized to the sulfone, and the PMB ether was removed to give alcohol **1.24**. Oxidation of the C19 alcohol to the ketone, removal of the C23 BOM ether, and a protection of the hemiketal intermediate produced methyl ketal **1.25**.

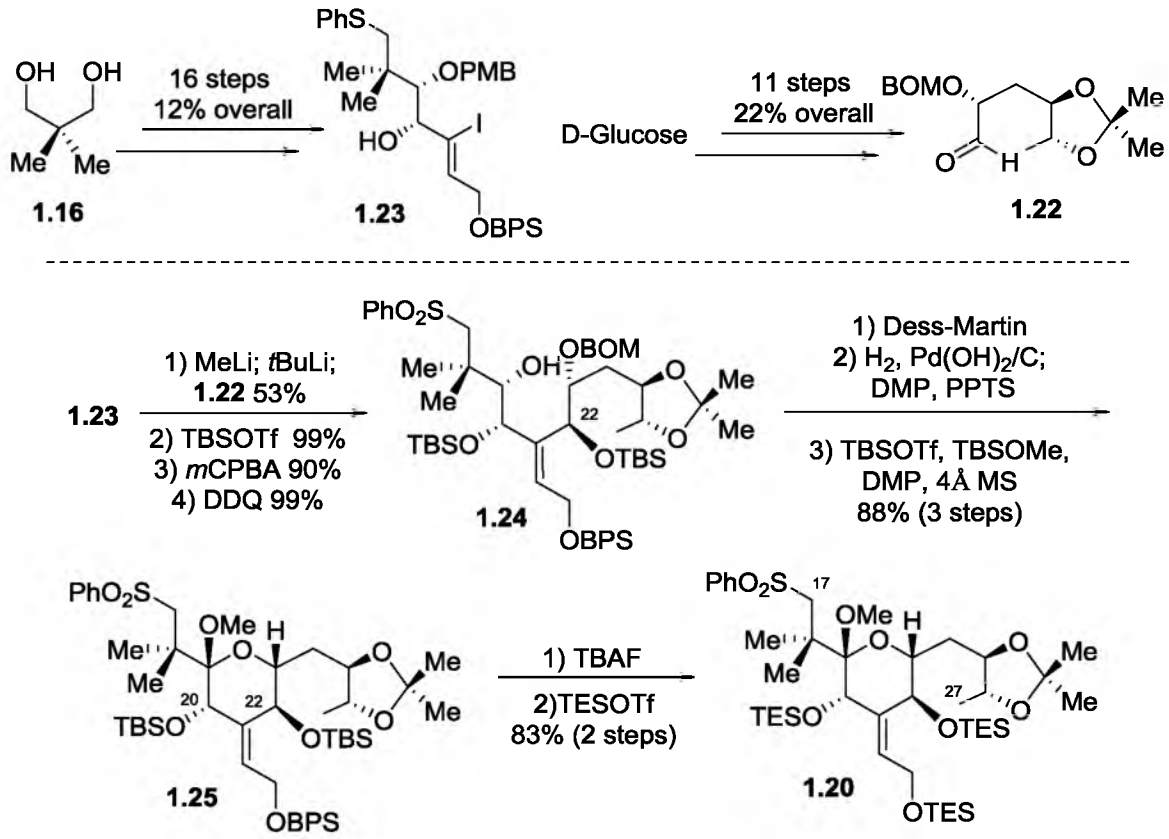


Figure 1.10. Synthesis of C-Ring Sulfone

A removal of all the silyl protecting groups and a reprotection as TES ethers was perfomered leading to the C17-C27 fragment **1.20**. Yamaura's group was able to construct the C-ring in 25 LLS and a total of 35 steps.

Wender's Total Synthesis of Bryostatin 9[54]

More recently in 2011, the Wender group completed the first total synthesis of bryostatin 9, which differs from bryostatin 7 only at the C20 ester position. A different approach was taken in this synthesis which applied a pyran annulation reaction[56], not the Julia olefination reaction, to join the northern and southern pieces (Figure **1.11**). This

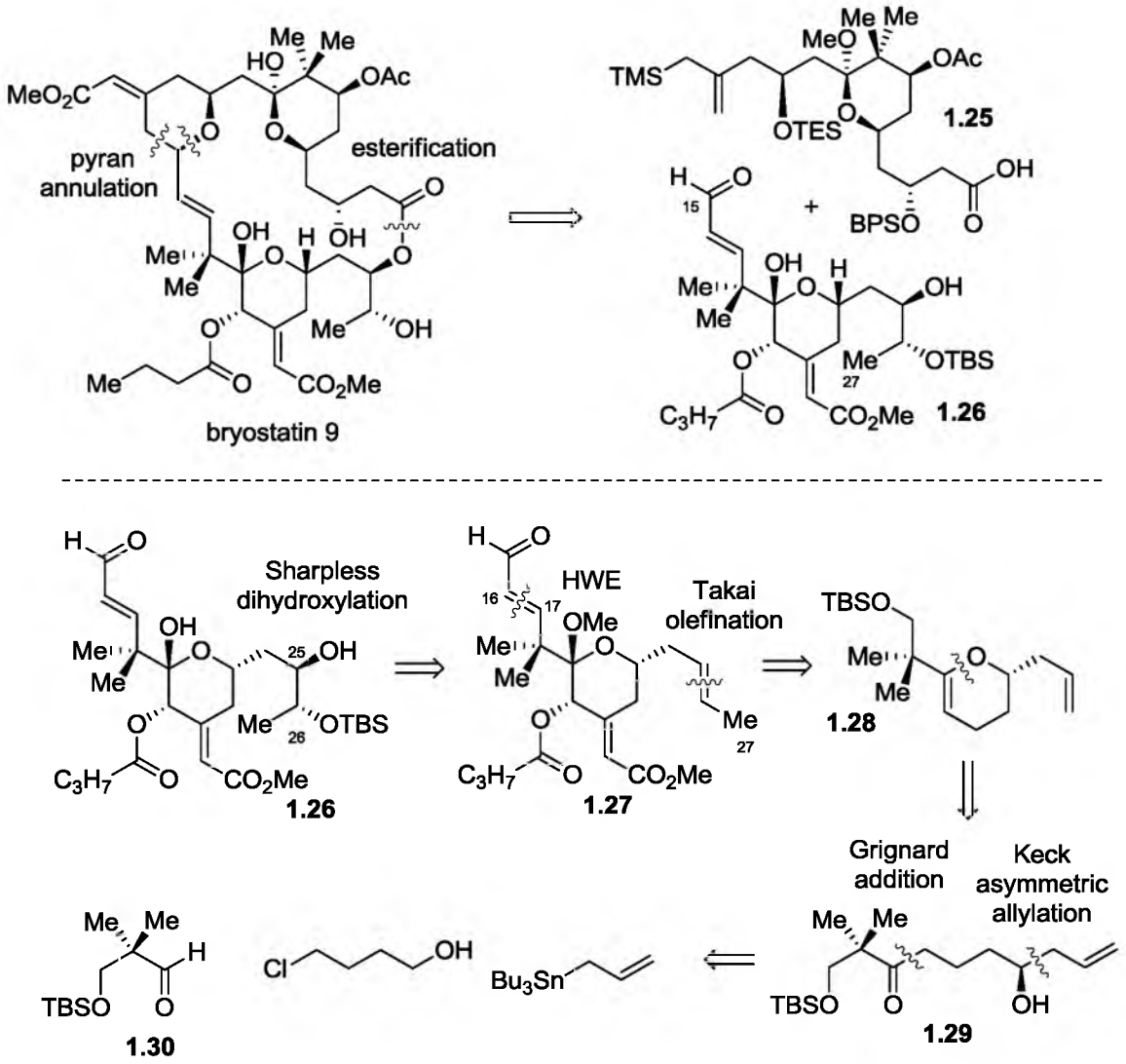


Figure 1.11. Wender's Retrosynthesis of Bryostatin 9

retrosynthetic approach had previously been shown to be a very convergent way to construct the bryostatin core and was first demonstrated on various bryostatin analogs.[57] The C26 and C25 stereocenters of C-ring **1.26** were to be set through a Sharpless asymmetric dihydroxylation from the corresponding olefin. The enal **1.27** was envisioned to be constructed through a Horner-Wadsworth-Emmons reaction and the C27 methyl group would be incorporated through a Takai olefination. The glycal **1.28** would be formed

through an acid mediated dehydrative cyclization reaction. Finally, the keto-alcohol **1.29** would be synthesized by a Grignard addition and catalytic asymmetric allylation.

The synthesis of C-ring **1.26** started with the monoprotection of 2-dimethylpropane-1,3-diol, followed by oxidation of the remaining alcohol to give aldehyde **1.30** (Figure **1.12**). The C19 aldehyde was then reacted with the Grignard reagent derived from 4-chloro-1-butanol. The C19 alcohol was oxidized and the subsequent aldehyde was subjected to Keck's asymmetric allylation conditions, giving homoallylic alcohol **1.29** with 92% ee. Dehydrative cyclization of keto-alcohol **1.29** with catalytic TsOH gave the glycal intermediate, followed by epoxidation and methanolysis with MMPP in MeOH. The resulting α-hydroxyl ketal was oxidized using TPAP/NMO to give C20 ketone **1.28**. The C26 methyl was then incorporated by oxidative cleavage with ozone, followed by Takai olefination to give olefin **1.31** as a 93:7 (*Z*:*E*) geometric mixture. Aldol condensation installed the C34 enoate using methyl glyoxylate and K_2CO_3 in MeOH. The C20 ketone was reduced using Luche conditions followed by esterification with butyric anhydride to give **1.32** as a single diastereoisomer at the C20 position. Desilylation, oxidation, and homologation with a vinyl zincate gave enal **1.27**. At this stage, the C26 and C25 alcohols were installed using Sharpless asymmetric dihydroxylation giving the diol **1.33** with a 4:1 dr. The methyl ketal was hydrolyzed using TsOH and the C26 alcohol was selectively silylated giving TBS ether **1.26**. The Wender group was able to construct the C-ring in a total of 19 linear steps, providing the shortest overall route to a functionalized C-ring. The highlight of this route was the Sharpless dihydroxylation which set 2 of the 4 stereocenters late stage.

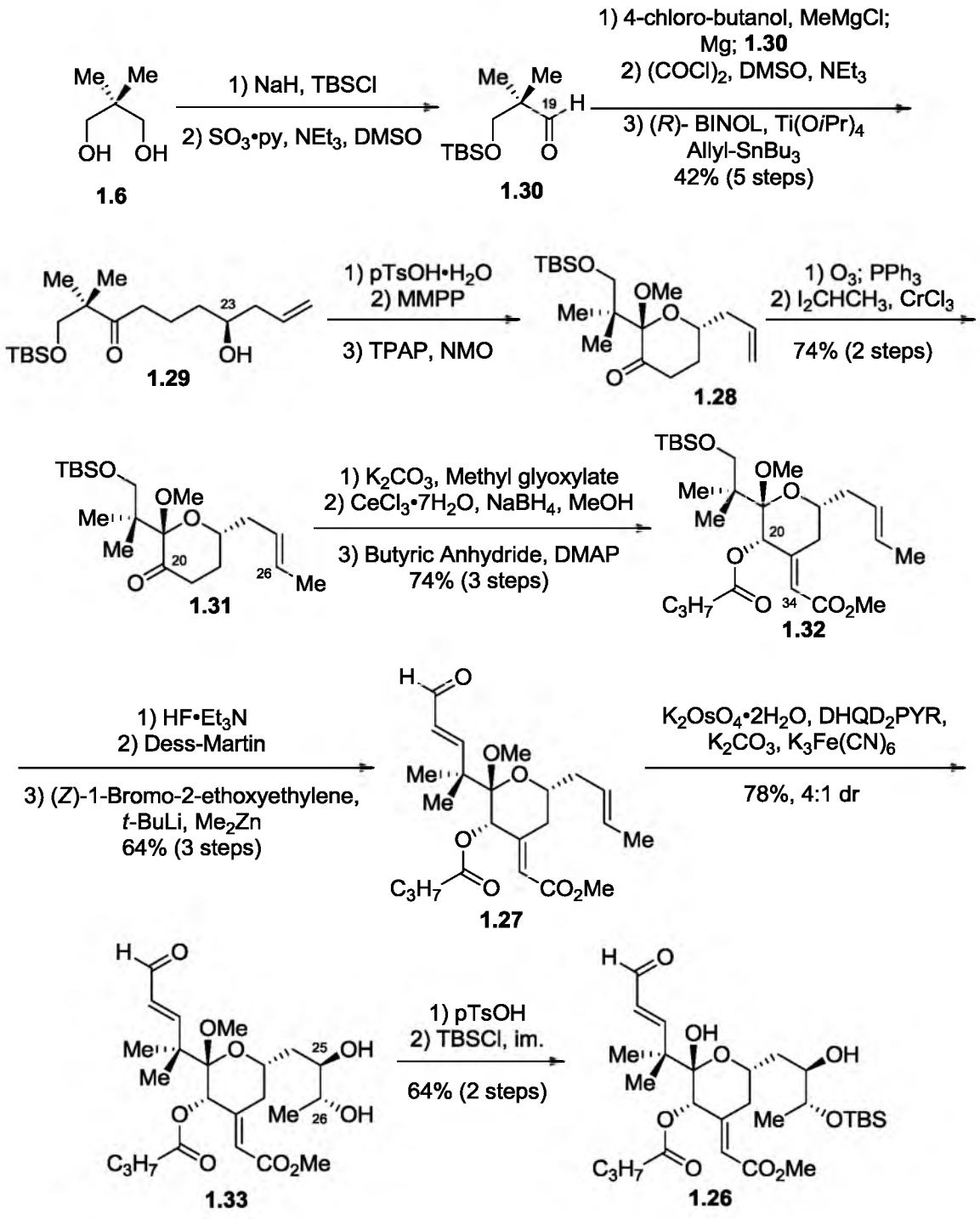


Figure 1.12. Synthesis of Functionalized C-ring

Krische's Total Synthesis of Bryostatin 7[55]

In 2011, the Krische group synthesized bryostatin 7. This was the most concise synthesis of a member of the bryostatin family to date due to the application of their C-C bond hydrogenation methodology to the construction of the A-ring portion **1.34** (10 steps).[55, 58] A convergent union between the A-ring **1.34** and C-ring **1.35** using the Keck pyran annulation reaction was envisioned followed by a Yamaguchi macrolactonization reaction to complete the 20-membered macrolactone (Figure **1.13**). The β-hydroxyallyl silane **1.36** was proposed to be incorporated through a Keck asymmetric allylation reaction. Intermediate **1.37** would be constructed through a convergent hydrogen mediated reductive coupling between glyoxal **1.38** and enyne **1.39**.

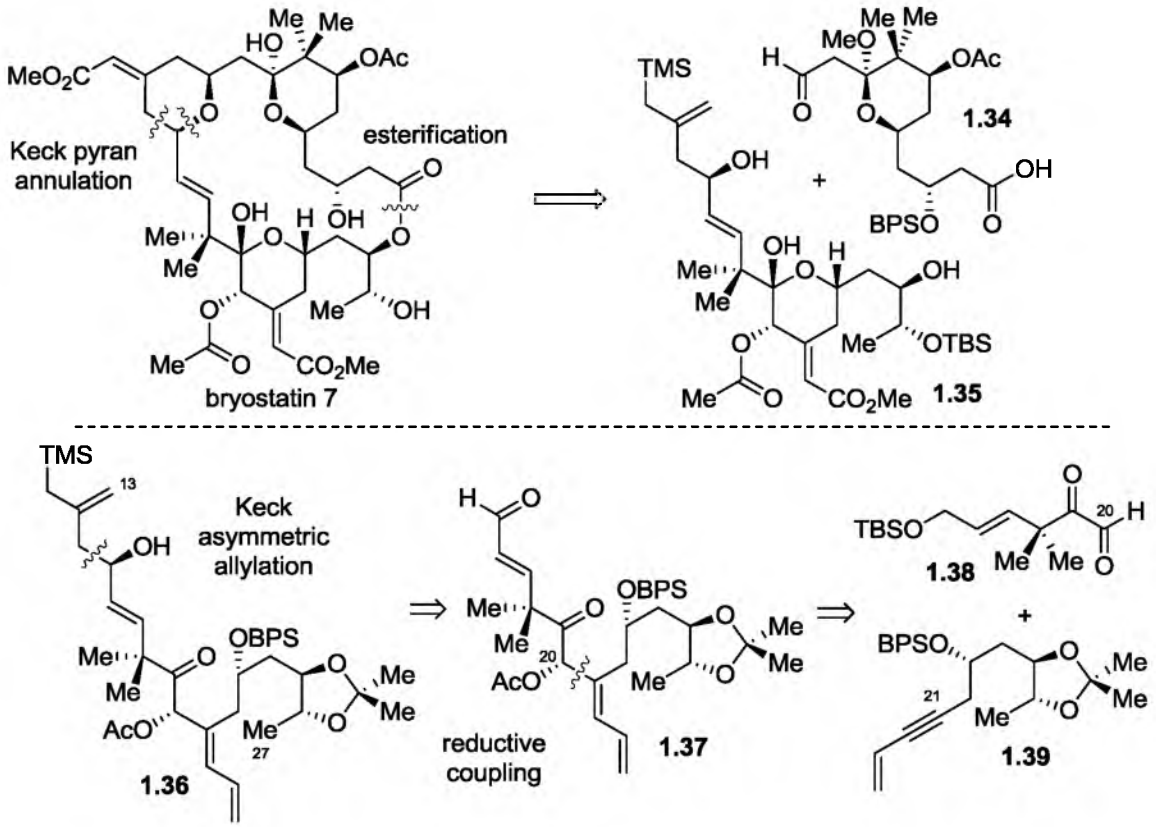


Figure 1.13. Krische's Retrosynthesis of Bryostatin 7

The synthesis of glyoxal **1.38** began with the hydroxymethylation of 3-methyl-butanone followed by a Swern oxidation of the resulting C17 alcohol to give ketoaldehyde **1.41** (Figure **1.14**). A Horner-Wadsworth-Emmons reaction using triethylphosphosphonoacetate then gave the C16-C17 α,β-unsaturated ester. The C19 ketone was transformed into the silyl enol ether and a same pot reduction of the ethyl ester with LAH provided allylic alcohol **1.45**. The C15 alcohol was then protected, as the TBS ether, and again in the same pot the enol ether was converted to the α-bromoketone with NBS. A Kornblum oxidation of the C20 completed the synthesis of glyoxal **1.38**.

Enyne **1.39** was derived from the dihydroxylation of crotononitrile giving the C25-C26 diol **1.44** in 86% enantiomeric excess. The diol was then protected as the acetonide and the nitrile was reduced to the aldehyde using DIBAL-H. A 1,3 chelation controlled reaction with propargyl zinc gave the C23 alcohol **1.45** as a 5:1 mixture of isomers. The C23 homopropargylic alcohol was protected as the BPS ether, followed by a Sonogashira reaction between the alkyne in **1.45** and vinyl bromide, giving enyne **1.39**.

The 1,3-enyne and glyoxal were coupled under hydrogen mediated reductive coupling to give C20 α-hydroxyketone **1.46** as a 7:1 mixture of diastereomers. These conditions proved to be very mild and did not over reduce the olefins in the desired product. The C20 acetate was then installed using acetic anhydride, the C15 silyl ether was removed, and the resulting alcohol was oxidized to give enal **1.37**. This aldehyde was reacted with trimethyl(2-((tributylstannyl)methyl)allyl)silane under modified Keck asymmetric allylation conditions to give C15 β-hydroxyallyl silane **1.36** as a single diastereomer by NMR.[59] The Krische group was able to construct the C-ring in 11 steps (LLS) and a total of 17 steps, showing a large improvement in making bryostatins C-ring.

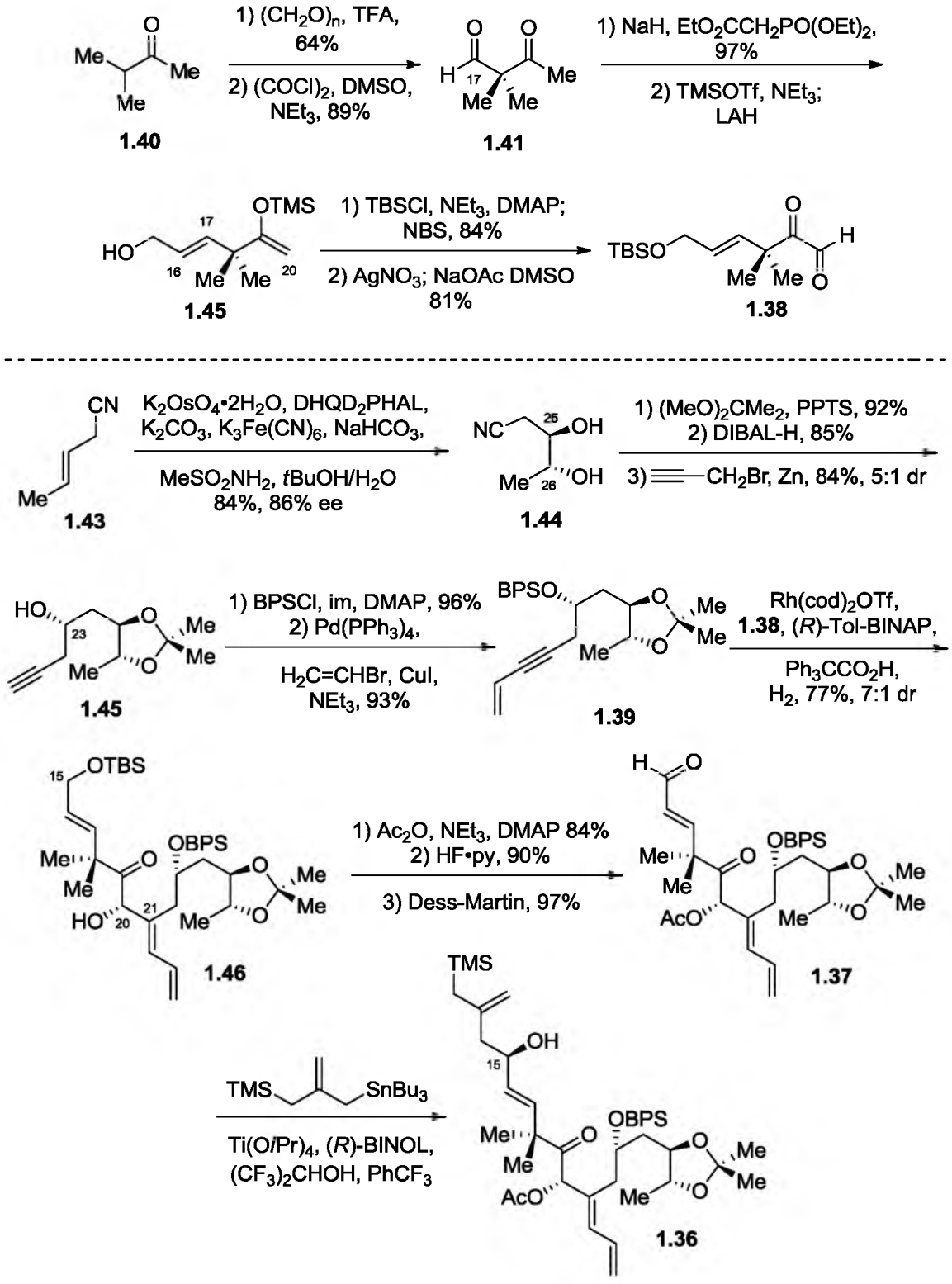


Figure 1.14. Synthesis of β-hydroxyallyl Silane **1.36**

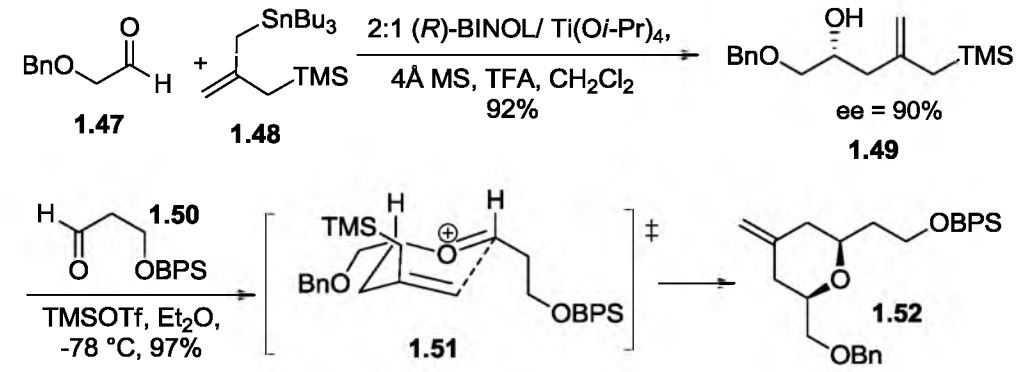
Results and Discussion

The Pyran Annulation Methodology

In 2002, an exceptionally facile enantioselective synthesis of 2,6-*cis*-disubstituted-4-methylenetetrahydropyran systems was reported in the effort toward the synthesis of bryostatin 1. In this paper, constructing β-hydroxyallyl silane **1.49** by a catalytic asymmetric allylation reaction of aldehyde **1.47** and trimethylsilyl methylallylstannane **1.48** is described (Figure **1.15**).[56] Dr. Covel found that treatment of a silane such as **1.49** and aldehyde **1.50** with TMSOTf results in the formation of the *2,6-cis*-disubstituted 4-methylene pyran **1.52** as a single *cis* isomer. The stereochemical outcome is in accord with a chair like transition state **1.51** where the alkyl groups are equatorially disposed.

Since this methodology's development, it has been used to construct many bryostatin analogs (Figure **1.15**). In Merle 23, the pyran annulation was used to construct both the A-ring and B-ring, establishing the exomethylene pyrans present in this analog.[57b, 60] These exocyclic olefins were oxidatively cleaved to ketones, reduced, and then esterified to give analog Merle 34.[61] Analogs resembling bryostatin 1, like Merle 30, were made using the pyran annulation and a late stage Horner-Wadsworth-Emmons reaction to give the α, β- unsaturated ester at the C13 position.[62] The pyran annulation methodology has also been successfully utilized by other groups such as the Wender group during the synthesis of bryostatin 9 [54] and bryostatin analogs,[63] and the Krische group during the synthesis of bryostatin 7.[55]

It was this versatile methodology which we thought would be the most convergent and useful way to construct bryostatin 1. Our first generation retrosynthesis of bryostatin 1 is shown in Figure **1.16**. The C-ring and B-ring would be functionalized from bryopyran



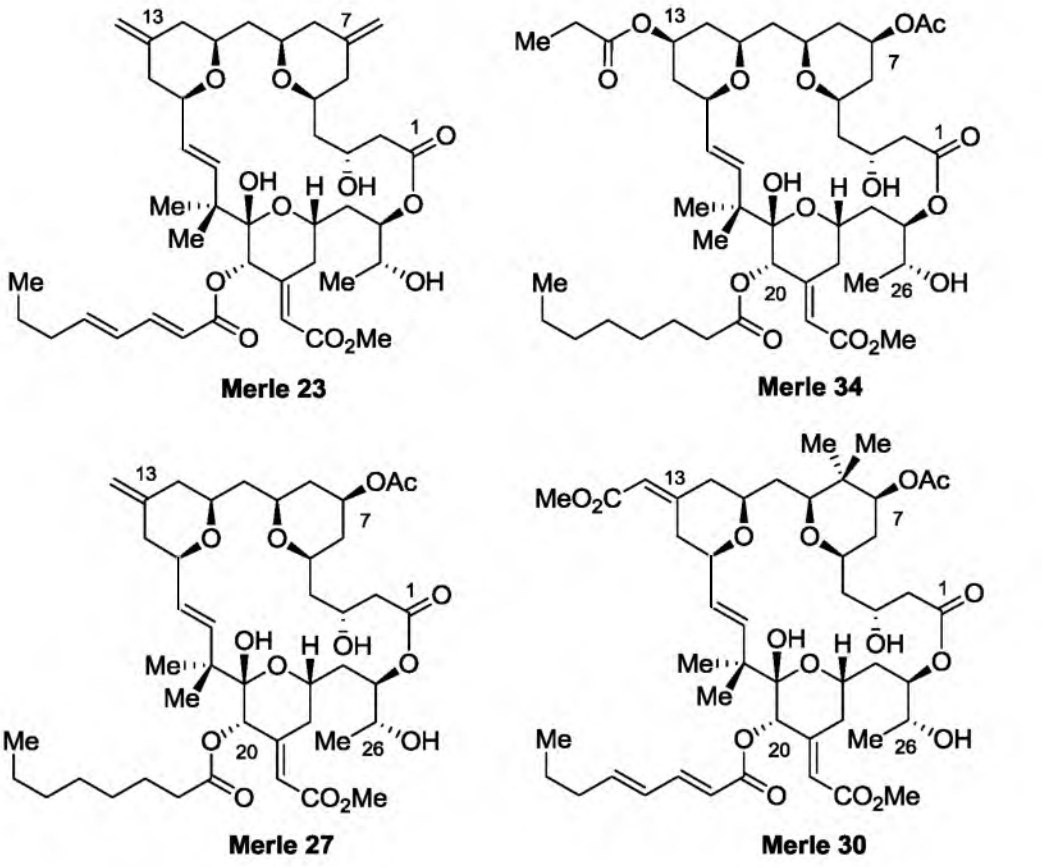


Figure 1.15. Pyran Annulation and Examples

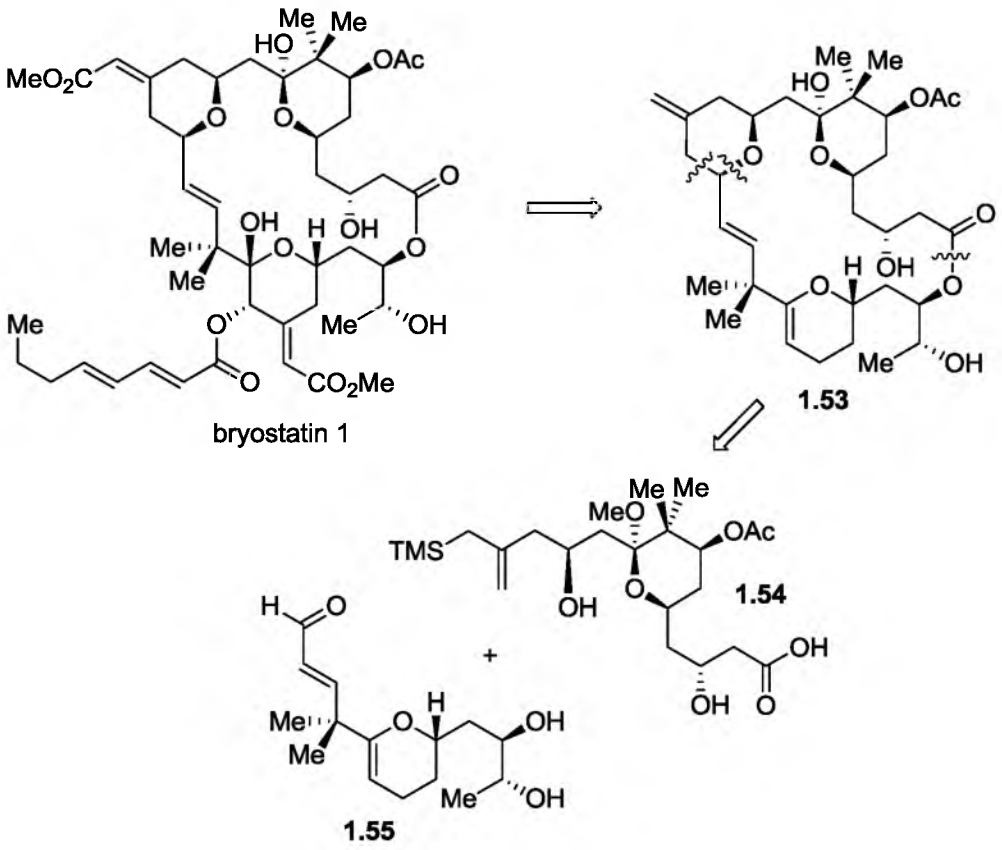


Figure 1.16. Retrosynthetic Analysis of Bryostatin 1

core **1.53** to give bryostatin 1. The B-ring of the tricycle was envisioned to be constructed from a pyran annulation between the A-ring aldehyde **1.55** and C-ring silane **1.54** using pyran annulation methodology. The 20 membered macrolactone would be completed using a Yamguchi macrolactonization.

The Problems with Late Stage C-ring Functionalization

Late stage functionalization of the C-ring was shown to very difficult during the synthesis of bryostatin analogs by Dr. Poudel (Figure **1.17**, part **A**). The aldol condensation between **1.56** and methyl glyoxylate at the C20 ketone could not be conducted selectively in the presence of the C7 acetate. This reaction provided a disappointing ratio of almost 1:1 desired to undesired aldol products **1.57** and **1.58** (Figure **1.17**, part **B**). Additionally, the Luche reduction of the C20 ketone in macrolactone **1.61** gave a somewhat less selective reaction (dr= 4:1) then had previously been observed. The Luche reduction on just the C-ring compound **1.59** was reported as a single diastereoisomer by our group.[64]

The Established C-ring Route and Associated Problems

The route shown in Figure **1.18** was developed by Dr. Anh Truong and was the standard method of producing the C-ring portion for our analog program.[65] The C27-C15 portion utilizes (*R*)-(+)-isobutyl lactate to set the stereochemistry of the C23 and C25 by chelation- controlled allylations to access **1.67** (Figure **1.18)**. The synthesis commenced with the BOM protection of alcohol **1.65** and a DIBAL-H half reduction of the C25 ester to give the aldehyde **1.64**. A 1,2-chelation controlled allylation reaction with allyltributyltin and $MgBr_2 \bullet Et_2O$ provided the C25 alcohol **1.65** as a single diastereomer. The resulting

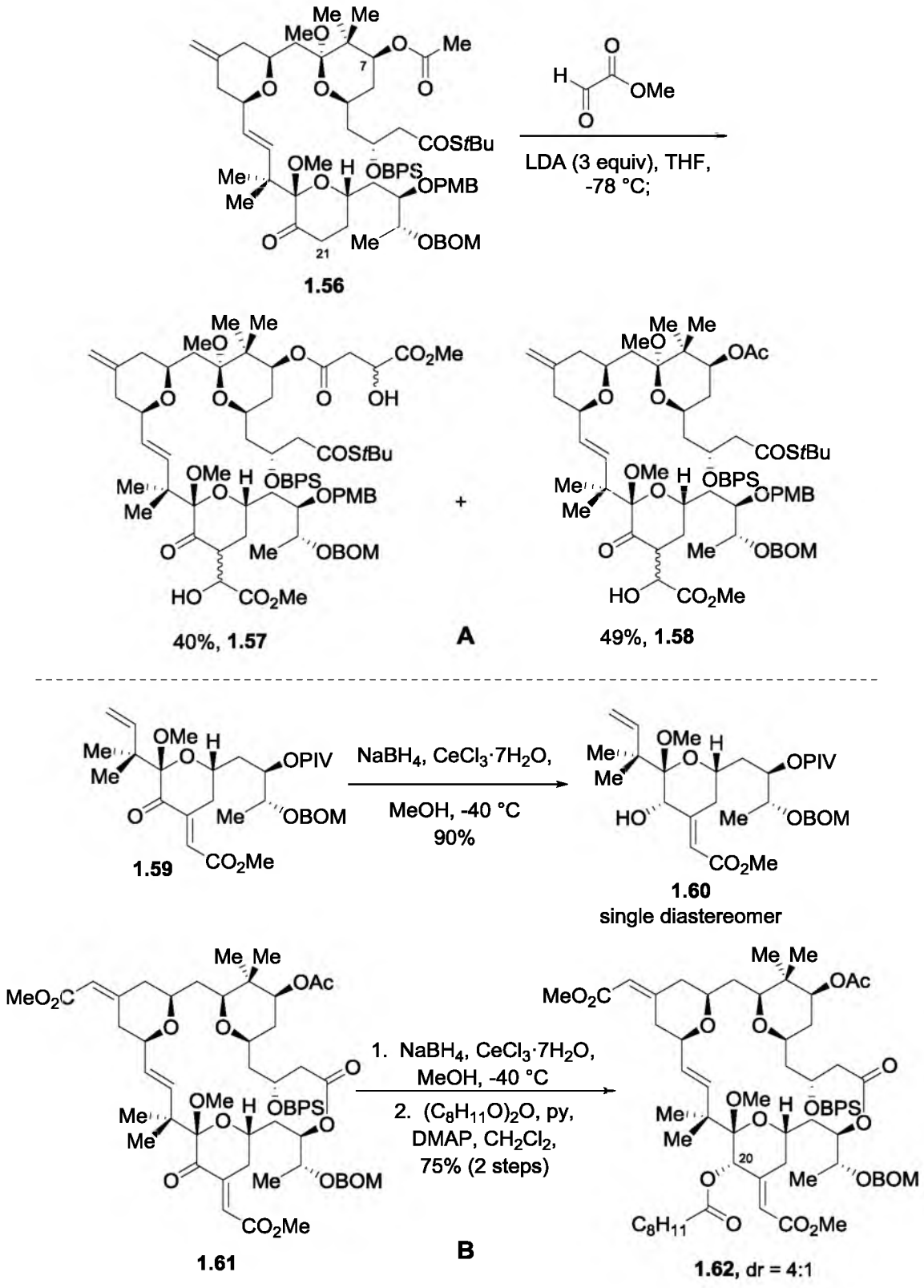


Figure 1.17. Unselective Aldol (A) and
Luche Reduction (B)

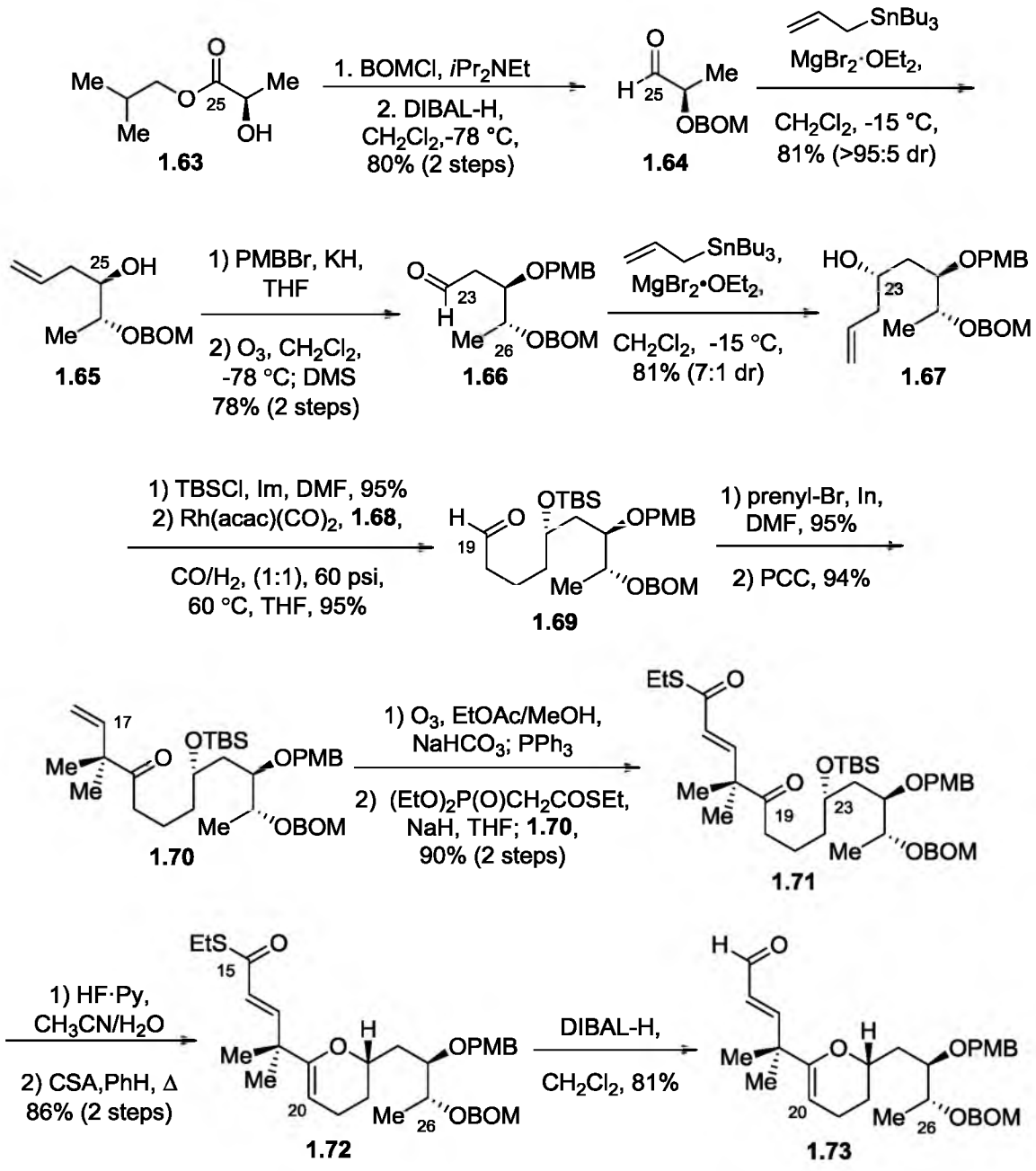


Figure 1.18. Synthesis of Glycal **1.73**

homoallylic C25 alcohol was PMB protected, followed by oxidative cleavage using ozonolysis to furnish aldehyde **1.66**. A second allylation reaction using $MgBr_2 \bullet Et_2O$ gave **1.67** as a 7:1 mixture of diastereomers. The synthesis of homoallylic alcohol **1.67** accomplished setting 2 stereocenters based on substrate control in 6 steps and was applicable to multigram-scale synthesis.

The homoallylic alcohol was further elaborated by a very practical synthesis shown in Figure **1.18**.[65] The C23 homoallylic alcohol **1.67** was protected as the TBS ether. A one carbon homologation using $Rh(acac)(CO)_2$ and phosphite ligand **1.68** under a CO/H_2 atmosphere provided aldehyde **1.69** in 95% yield. Treatment of C19 aldehyde **1.72** with a prenyl indium reagent delivered the alcohol in 95% yield. The hindered alcohol was then oxidized with a combination of PCC and NaOAc to give ketone **1.70**. Ozonolysis of the terminal olefin delivered the aldehyde, which was then subjected to a Horner-Wadsworth-Emmons conditions reaction to give the desired α,β-unsaturated thiol ester **1.71**. Deprotection of the TBS ether using HF•py was followed by cyclization to give the desired glycal **1.72** in 89% yield. Finally, a half reduction using DIBAL-H would give us the desired enal **1.73**. The C-ring was constructed in a total of 15 steps and was comparable in length to the Evans' C-ring synthesis (16 steps). This route would allow for the convergent connection between the C- ring and A-ring while forming the B-ring through a pyran annulation reaction, but it does not incorporate the C-ring functionality at the C19, C20, and C21 positions.

Attempts at a fully functionalized C-ring aldehyde are summarized in Figure **1.19**. Setting the C19 stereocenter and oxidizing the C20 alcohol were accomplished by epoxidizing the enol ether with *m*CPBA, which underwent methanolysis, giving the

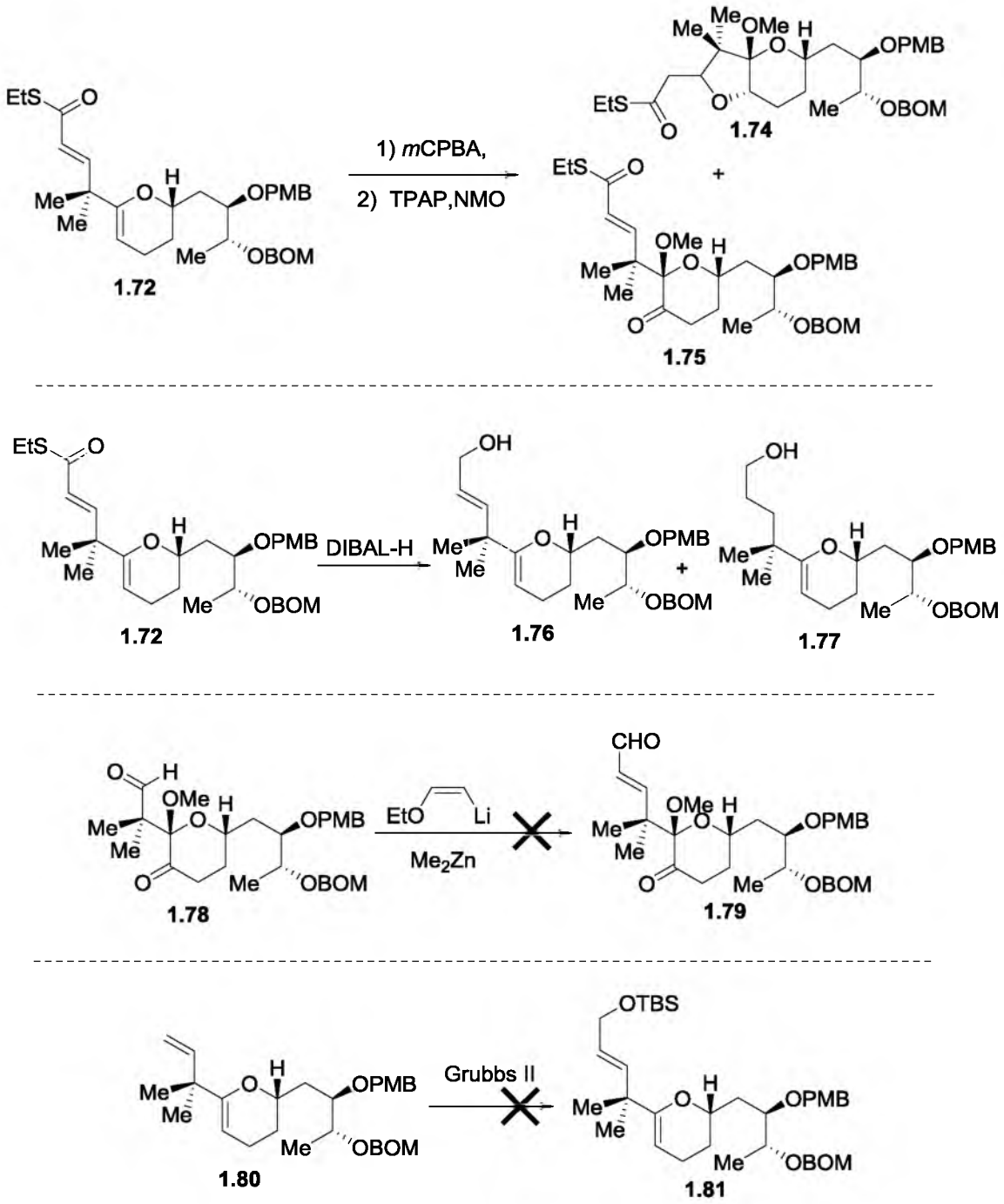


Figure 1.19. Problems Functionalizing the C-ring

anomeric α-hydroxyl ketal **1.75**. Unfortunately a major side product **1.74** was formed by a Michael addition of the resulting C19 alcohol to the α, β-unsaturated thioester.[66] A full reduction of this thioester and protection of resulting alcohol was attempted to circumvent this side reaction, but a 4:1 ratio of products **1.76** and **1.77** was observed.[62a] Attempts to elongate hindered aldehyde **1.78** with various nucleophiles like a vinyl zincate[65] or cross metathesis of olefin **1.81** were unsuccessful, potentially due to the steric hindrance caused by the *gem*-dimethyl group.[62a]

The Retrosynthetic Analysis of Bryostatin 1

The use of fully functionalized C-ring **1.83** would allow us to avoid the late stage problematic steps and would make the synthesis much more convergent. Additionally, this would eliminate the linear nature of the original retrosynthetic analysis. Our synthetic plan would combine the A-ring **1.82** and C-ring **1.83**, which are almost equal in complexity, through a pyran annulation and a Yamaguchi macrolactonization (Figure **1.20**).

A Convergent Route to the C-ring[53]

Although glycal **1.73** could be prepared on a gram scale, frequent requirement of this material in multigram quantities for all bryostatin projects demanded a more concise synthesis. The drawbacks of the route to glycal **1.73** were its linear nature and the earlyinstallment of the α, β- unsaturated thioester. Thus, a simple improvement to this route would be to make it more convergent and to unmask the C15-C17 α, β- unsaturated aldehyde only prior to pyran annulation. This cyclic enol ether **1.86** was envisioned to be formed through a very versatile methodology developed by the Rainier group and has

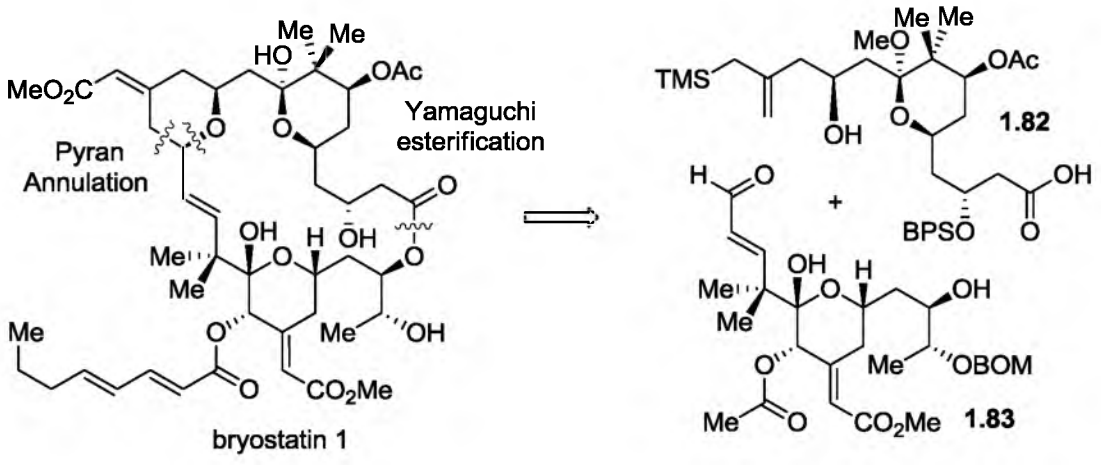


Figure 1.20. Retrosynthetic Analysis of Bryostatin 1

been used successfully during the synthesis of various natural products such as brevenal[67] and gambierol.[68]

The retrosynthetic analysis of the C-ring is shown in Figure **1.21**. The C-ring exocyclic enoate could be incorporated from ketone **1.85** via an aldol condensation with methyl glyoxylate, which was previously described by the Wender and Evans groups.[50b, 69] A reduction of this ketone from the less hindered face would establish the stereocenter at the C20 position. The C19 stereocenter would be set by an oxidation of the enol ether and subsequent methanolysis, giving a α-hydroxyl ketal from the dihydropyran **1.86**. The cyclic enol ether **1.86** was to be constructed using a Rainier metathesis reaction. Ester precursor **1.87** was to be made through a convergent union of carboxylic acid **1.88** and alcohol **1.89.** The carboxylic acid piece **1.88** would be made from commercially available methyl isobutyrate (Figure **1.22**).

Methyl isobutyrate was alkylated with allyl bromide to give ester **1.92**. A Wohl-Zeigler bromination using benzoylperoxide and *N*- bromosuccinimide in CCl_4 produced allylic bromide **1.92** with a 70% yield.[70] Silver triflate-assisted substitution with TBS

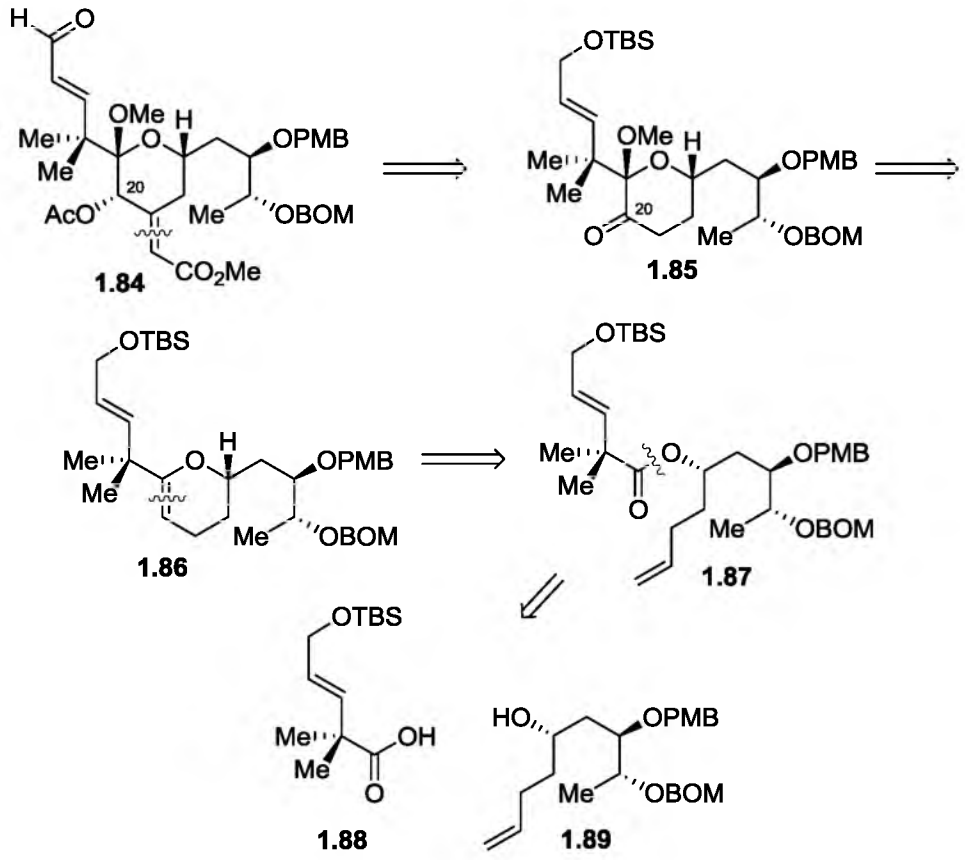


Figure 1.21. Retrosynthesis of the C-ring

silanol gave silyl ether **1.93**. Finally, careful hydrolysis of the methyl ester at 0 °C delivered carboxylic acid **1.88** in 93% yield in the presence of the terminal TBS ether.

At this point, an investigation into constructing alcohol **1.89** was conducted. Aldehyde **1.66** was synthesized on a multigram scale according to the previously described route.[65] Asymmetric induction using a 1,3-chelation controlled Grignard addition to an aldehyde are previously reported in the literature, but they are not common. Our group has observed that the removal of THF from vinyl magnesium bromide under high vacuum and replacing the solvent with CH_2Cl_2 increases diastereoselectivity of Lewis acid mediated Grignard additions.[71] This was further emphasized by Dr. Rudra's discovery of a 1,3-

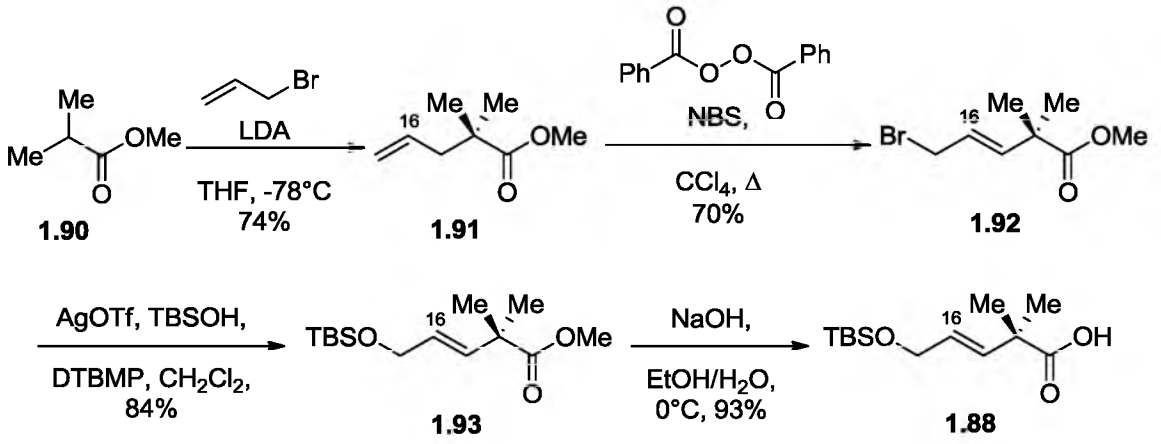
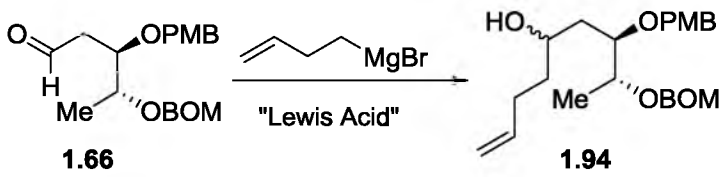


Figure 1.22. Synthesis of Acid Subunit

chelation controlled addition of vinyl magnesium bromide into a 1,3-PMB ether aldehyde with Me_2AlCl in toluene, giving a 10:1 dr.[61a] Subjecting aldehyde **1.66** to alkyl Grignard addition under various Lewis acid conditions (Figure **1.23**) resulted in only modest selectivity for the addition, with the highest diastereoselectivity (*dr* ~2:1) seen when using $MgBr_2 \bullet Et_2O$ in THF, toluene, or CH_2Cl_2. With these disappointing results, other options were explored.

An alternative method is shown in Figure **1.24**. Subjecting aldehyde **1.64** to a 1,2 chelation controlled Mukaiyama aldol addition using TMS enol ether **1.95** gave ketone **1.96** as a 11:1 mixture of diastereomers. The next step was to reduce the β-hydroxy ketone using the Evans-Tishchenko reaction with SmI_2 to provide *anti* 1,3-diol, but unfortunately this reduction did not work even with stoichiometric amounts of SmI_2. A similar lack of reactivity was observed by the Evans group on a δ-benzoxy-β-hydroxy ketone.[72]

Our inability to produce **1.89** led us to homologate the olefin after esterification (Figure **1.25**). Alcohol **1.67** was synthesized on a multigram scale utilizing a previously developed procedure.[65] With both fragments in hand, carboxylic acid **1.88** and alcohol **1.67**



1.66 **1.94**

Conditions	Result
THF, -78°C	dr = 1:1
$MgBr_2 \bullet OEt_2$, THF, -78°C	dr = 2:1
$MgBr_2 \bullet OEt_2$, PhMe, -78°C	dr = 2:1
$MgBr_2 \bullet OEt_2$, CH_2Cl_2, -78°C	dr = 2:1
$TiCl_4$, CH_2Cl_2, -78°C	multiple products
$Ti(O^iPr)_4$, CH_2Cl_2, -78°C	dr = 1:1
Me_2AlCl, THF, -78°C	dr = 1:1
Me_2AlCl, PhMe, -78°C	dr = 1:1
Me_2AlCl, CH_2Cl_2, -78°C	dr = 1:1
$SnCl_4$, THF, -78°C	multiple products

Figure 1.23. Grignard Addition Conditions

were coupled using a Steglich esterification with EDCI and DMAP to give the desired ester **1.98**. Initially this reaction gave poor results; carboxylic acid **1.88** was being converted to the *N*-acyl urea by-product. The use of DMAP▪HCl under highly concentrated conditions suppressed the formation of the by-product, giving ester **1.87** in an 87% yield. One carbon homologation of olefin **1.98** began with hydroboration /oxidation. Reaction of the olefin with borane/dimethylsulfide proved to be unselective between the C20 and C16-

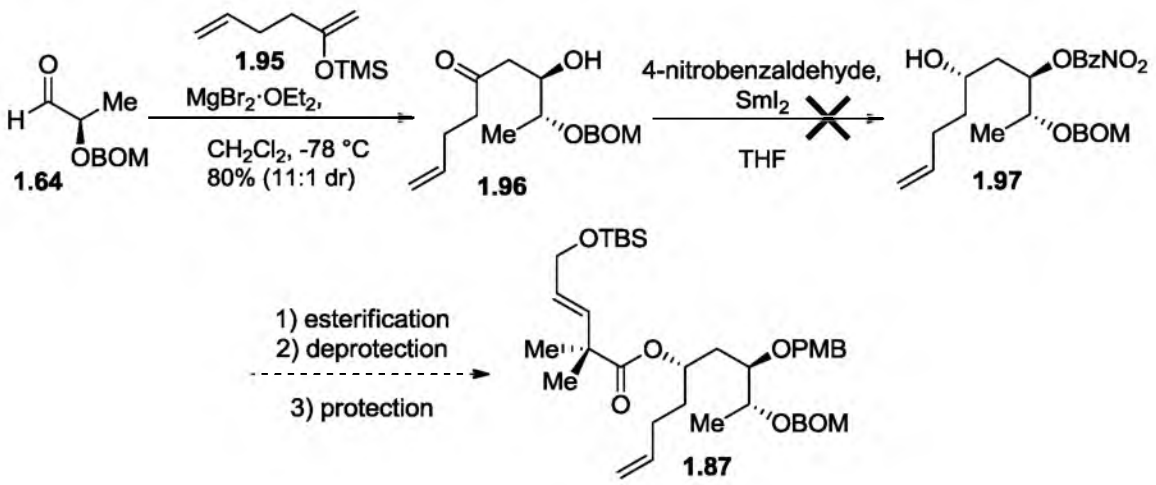


Figure 1.24. Evans- Tishchenko Reduction

C17 olefins and 9-BBN was unreactive under normal conditions. Fortunately, applying ultrasound to the 9-BBN reaction resulted in a rapid conversion, giving the C20 primary alcohol **1.99** in a 74% yield after oxidation with H_2O_2 and NaOH.[73] The resulting alcohol was oxidized using Parikh-Doering conditions, and Wittig olefination gave the desired one carbon extended olefin **1.87** in good yields.

The Rainier titanium-induced ring closing metathesis (RCM) reaction conditions smoothly delivered cyclic enol ether **1.86** in an 80% yield (Figure **1.26**).[74] It is postulated that this reaction works so well because the *gem*-dimethyl group is located adjacent to the carbonyl group creating an unfavorable steric interaction with the titanium ethylidene. This eliminates the undesired acyclic product **1.102** and gives us only cyclic enol ether **1.86**. Functionalizing the C-ring began with setting the C19 stereocenter by epoxidation of enol ether **1.86** with MMPP in MeOH, giving the anomeric α-hydroxyl ketal (Figure **1.27**).[75] This was immediately oxidized, without column chromatography, using Ley conditions to afford ketone **1.85** in 66% over 2 steps. An aldol condensation with ketone **1.85** and freshly

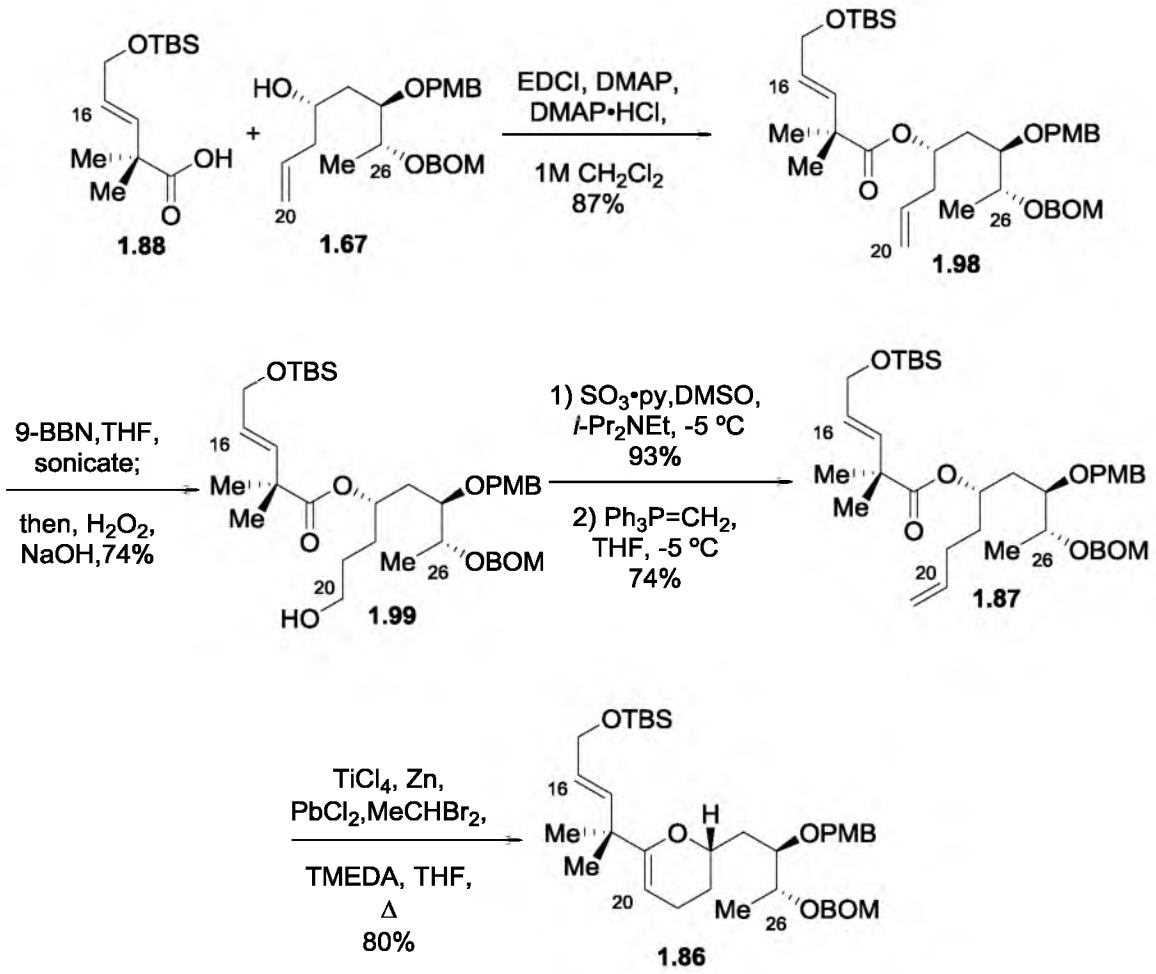


Figure 1.25. Synthesis of Glycal **1.86**

prepared methyl glyoxylate in the presence of K_2CO_3 delivered the C21 *E*-enoate **1.103** with an 82% yield. A Luche reduction from the less hindered face of the C20 ketone afforded the alcohol intermediate, which was quickly esterified with acetic anhydride to provide ester **1.104** in an 84% yield over 2 steps.

This newly formed ester group would serve as a protecting group during the synthesis of bryostatin 1. We hypothesized that the C20 acetate would be more electrophilic and less sterically hindered than the C7 ester, which would allow us to remove

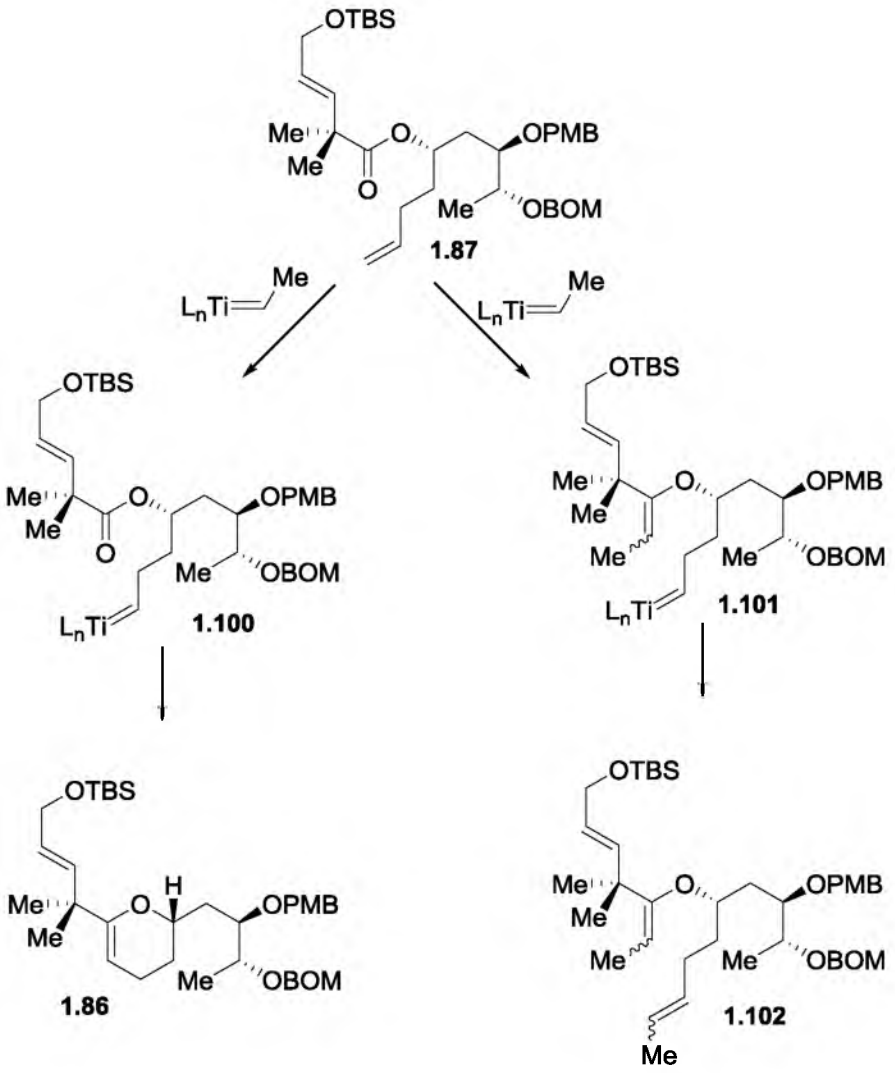


Figure 1.26. Cyclic vs. Acyclic Pathway for Rainier RCM

one in the presence of the other to introduce the bryostatin 1 side chain later on in the synthesis. [60] In order to couple the C-ring with the A-ring through a pyran annulation, the TBS ether was removed using HF·py and the resulting allylic alcohol was oxidized using Ley conditions furnishing enal **1.84**. The result of this newly described synthesis provided the most convergent and concise way to construct a highly functionalized C-ring at the time. The C-ring was constructed in 18 steps (LLS) and a total of 22 steps.

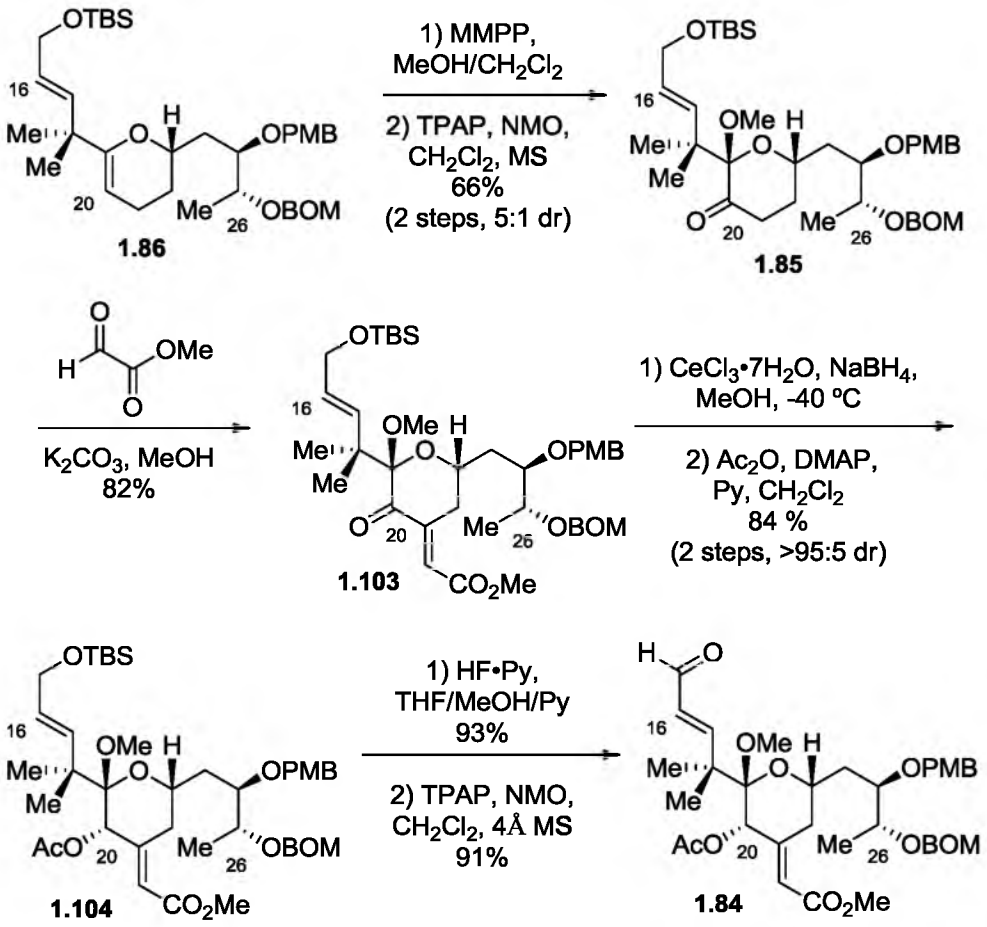


Figure 1.27. Synthesis of Fully Functionalized C-ring

The Construction of the A-ring[76]

Our A-ring synthesis was developed by Dr. Welch, and is based on chelation controlled allylations guided by a stereocenter set by a Keck asymmetric allylation reaction (Figure **1.28**).[76] It was envisioned that the A-ring would be constructed through a cyclization reaction of hydroxyketone **1.106**. This acyclic precursor was to be constructed using our Lewis acid mediated 1,3-addition of stannane **1.107** into aldehyde **1.108**, which would set the C7 stereocenter. Prenyl stannane **1.107** would be prepared from

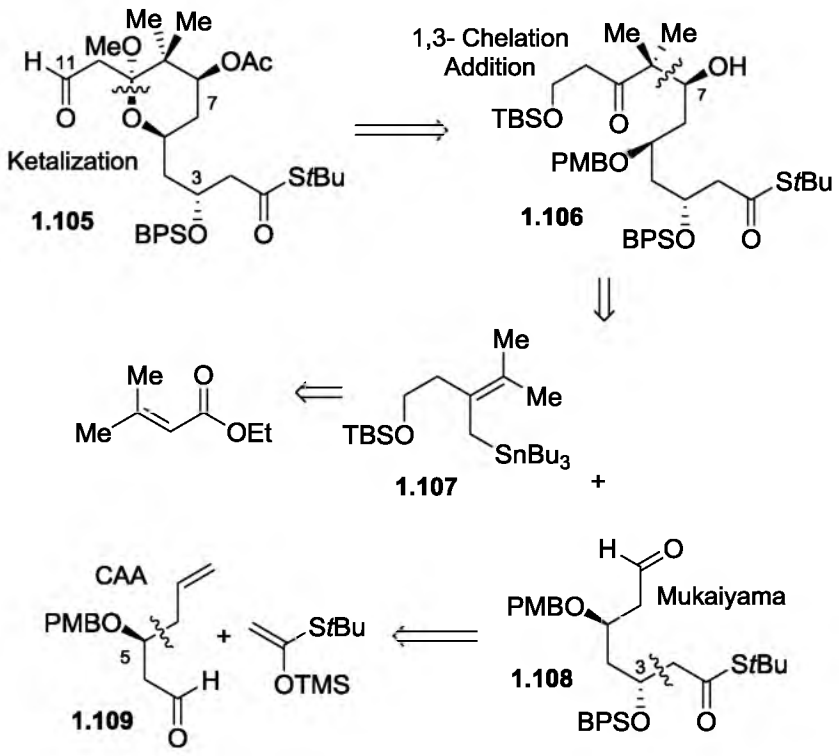


Figure 1.28. Retrosynthesis of A-ring Aldehyde

commercially available ethyl 2, 2-dimethyl acrylate. The C3 stereocenter in **1.108** was planned to be established using a chelation controlled Mukaiyama addition of thioketene acetal into aldehyde **1.109**, which in turn would be prepared using a CAA (catalytic asymmetric allylation) reaction to set the C5 stereocenter.

The construction of prenyl stannane **1.107** started from commercially available acrylate **1.110** (Figure **1.29**, part **A**). The sequence began with a vinylogous alkylation of the enolate using TBS ether protected 2-iodoethanol, providing **1.111**. Migration of the olefin using potassium *tert*-butoxide gave the thermodynamically favored α,β-unsaturated ester **1.112**. The ethyl ester was reduced to alcohol **1.112**, which was then mesylated, followed by an *in situ* displacement with tributyltinlithiate to give prenyl stannane **1.107**.

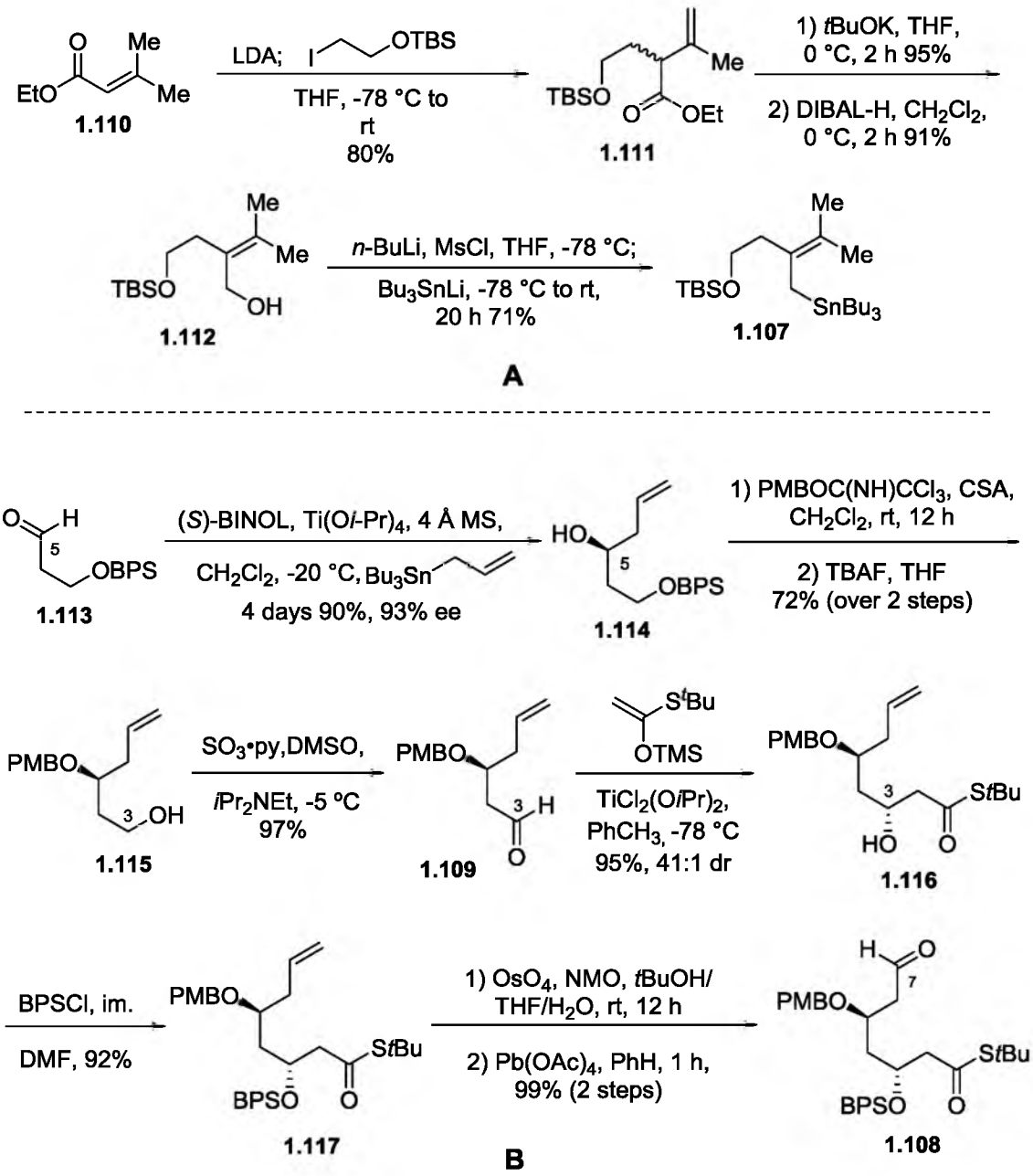


Figure 1.29. Synthesis of Prenyl Stannane **1.107** (A) and A-ring Aldehyde **1.108** (B)

The synthesis of aldehyde **1.108** (Figure **1.29**, part **B**) began with a catalytic asymmetric allylation of aldehyde **1.113**, giving homoallylic alcohol **1.114** with a 93% ee. The C5 alcohol was then protected as the PMB ether, which was chosen to facilitate a 1,3-chelation controlled allylation. The BPS ether was removed using TBAF and the resulting alcohol was oxidized using Parikh-Doering conditions to give aldehyde **1.109**. After scrupulous optimization, the use of 2.5 equiv of $TiCl_2(O\textit{i}Pr)_2$ afforded a 95% yield of aldol product **1.116** as a 41:1 mixture of diastereomers. The C3 β-hydroxy thioester **1.116** was protected as the BPS ether and the terminal olefin was oxidatively cleaved to give aldehyde **1.108**.

With the prenyl stannane and aldehyde in hand, the critical chelation controlled addition reaction was attempted (Figure **1.30**). Nucleophilic addition of stannane **1.107** using excess Me_2AlCl into aldehyde **1.108** delivered alcohol **1.106** as a single diastereoisomer in 86% yield. This crucial reaction manages to set the C7 stereocenter and installs the *gem*-dimethyl group. Acyclic intermediate **1.106** was acetylated at the C7 hydroxyl and the C5 PMB ether was removed with DDQ providing intermediate **1.118**. Ozonolysis gave lactol **1.119** as the sole product with no open chained keto-alcohol observed. Treatment of this lactol under acidic methanol conditions protected the hemiketal as the methylketal and simultaneously removed the TBS ether, providing the primary alcohol. Subsequent Parikh-Doering oxidation produced desired aldehyde **1.105**.

At this point, Dr. Poudel investigated ways to incorporate the β-hydroxyallylsilane from aldehyde **1.105**.[77] Unfortunately, a catalytic asymmetric allylation reaction failed to produce any product even with high catalyst loading. Since a direct asymmetric incorporation of the silane failed, a slightly longer approach was found to work well (Figure

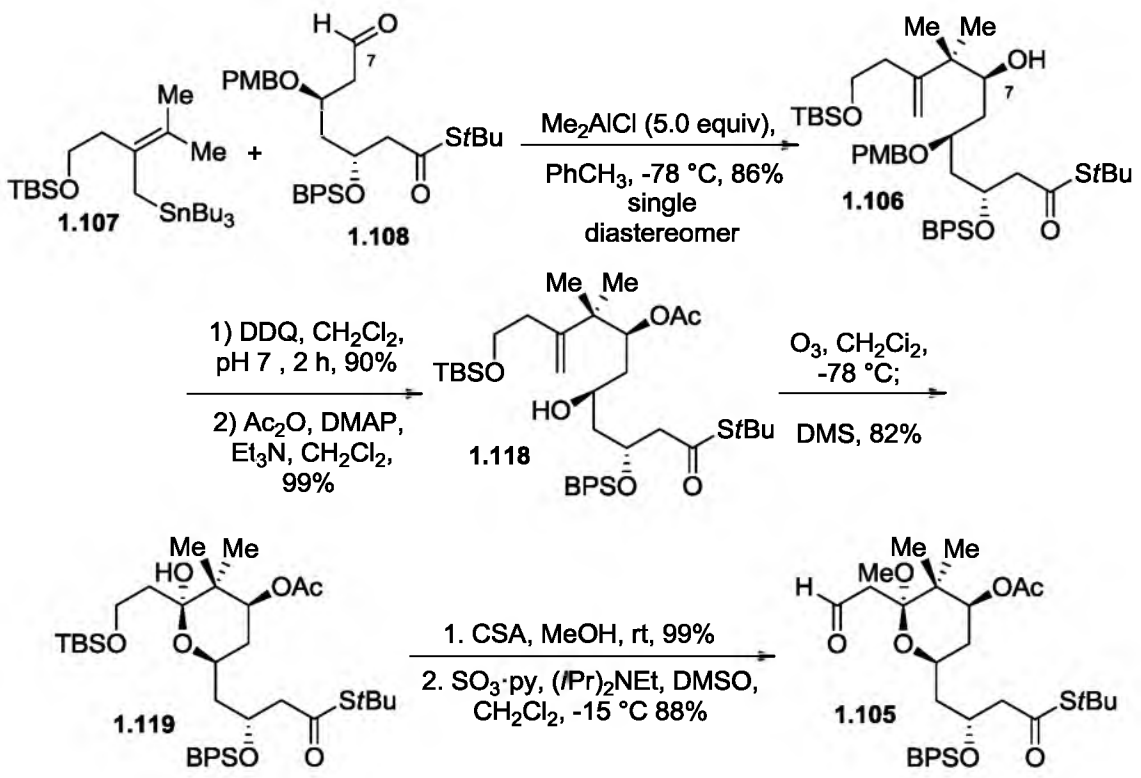


Figure 1.30. Synthesis of A-ring Aldehyde **1.105**

1.31). This approach started off with a thermal addition of trimethylsilyl methylallylstannane into aldehyde **1.105** to produce β-hydroxyallylsilane **1.120** as a 1:1 mixture of diastereomers, followed by a Parikh-Doering oxidation affording ketone **1.121**. After screening a short list of reducing agents, Luche conditions gave the desired β-hydroxyallylsilane **1.122** with a moderate 4:1 diastereoselectivity at the C11 center.

The Completion of Bryostatin 1 and Bryostatin 7 [53, 78]

Bryostatin 1 and 7 were both completed by Dr. Poudel, and are described in the following sections. With the fully functionalized C-ring aldehyde **1.84** and β-hydroxyallylsilane **1.122** (Figure **1.32**), the pyran annulation reaction provided the tricyclic

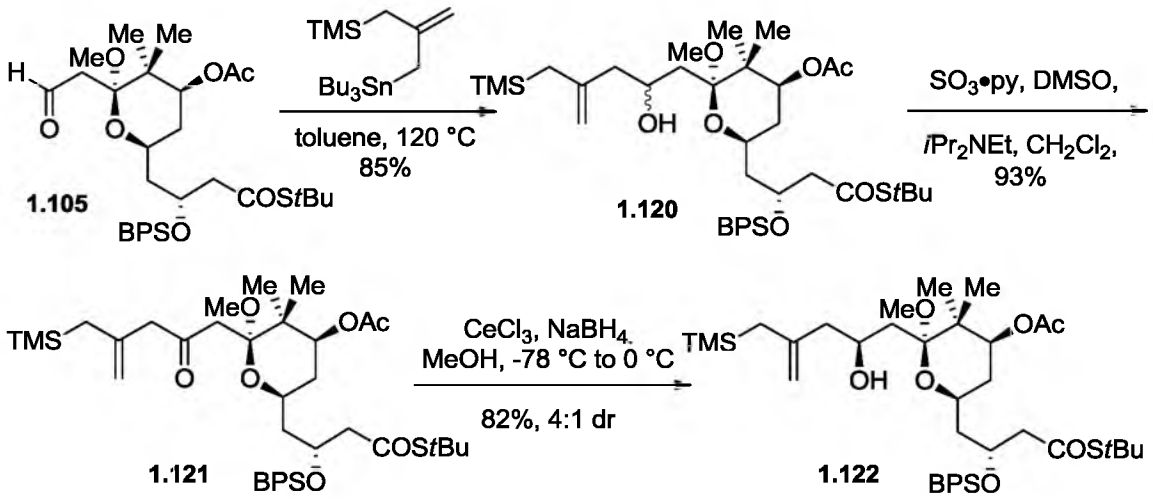


Figure 1.31. Synthesis of A-ring Silane **1.122**

bryopyran core in 61% yield. Unfortunately, a major side product caused by an intramolecular cyclization at C9, producing a spirocyclic product, diminished the yield of the pyran annulation reaction. In order to remove the thioester, a combination of the removal of the C3 BPS ether with HF•py followed by $LiOH/H_2O_2$ was necessary to produce acid **1.125**.[79] Not removing the C3 BPS rendered the thioester **1.123** inactive under these same conditions.[77] The C3 hydroxy group was protected as the TES ether, the PMB was removed using DDQ, and the macrolactone was completed using Yamaguchi conditions, giving **1.126**.[80] At this point, the basic structure of bryostatin 1 was intact, and only needed a few modifications on the C-ring and B-ring and a global deprotection to be complete.

The final steps and completion of bryostatin 1 are shown in Figure **1.33**. The B-ring was elaborated using Sharpless asymmetric dihydroxylation, followed by sodium periodate cleavage to furnish C13 ketone **1.127**. A Horner-Wadsworth-Emmons reaction on this ketone using Fuji's chiral BINOL phosphonate **1.128**[81] provided a 4:1 mixture of

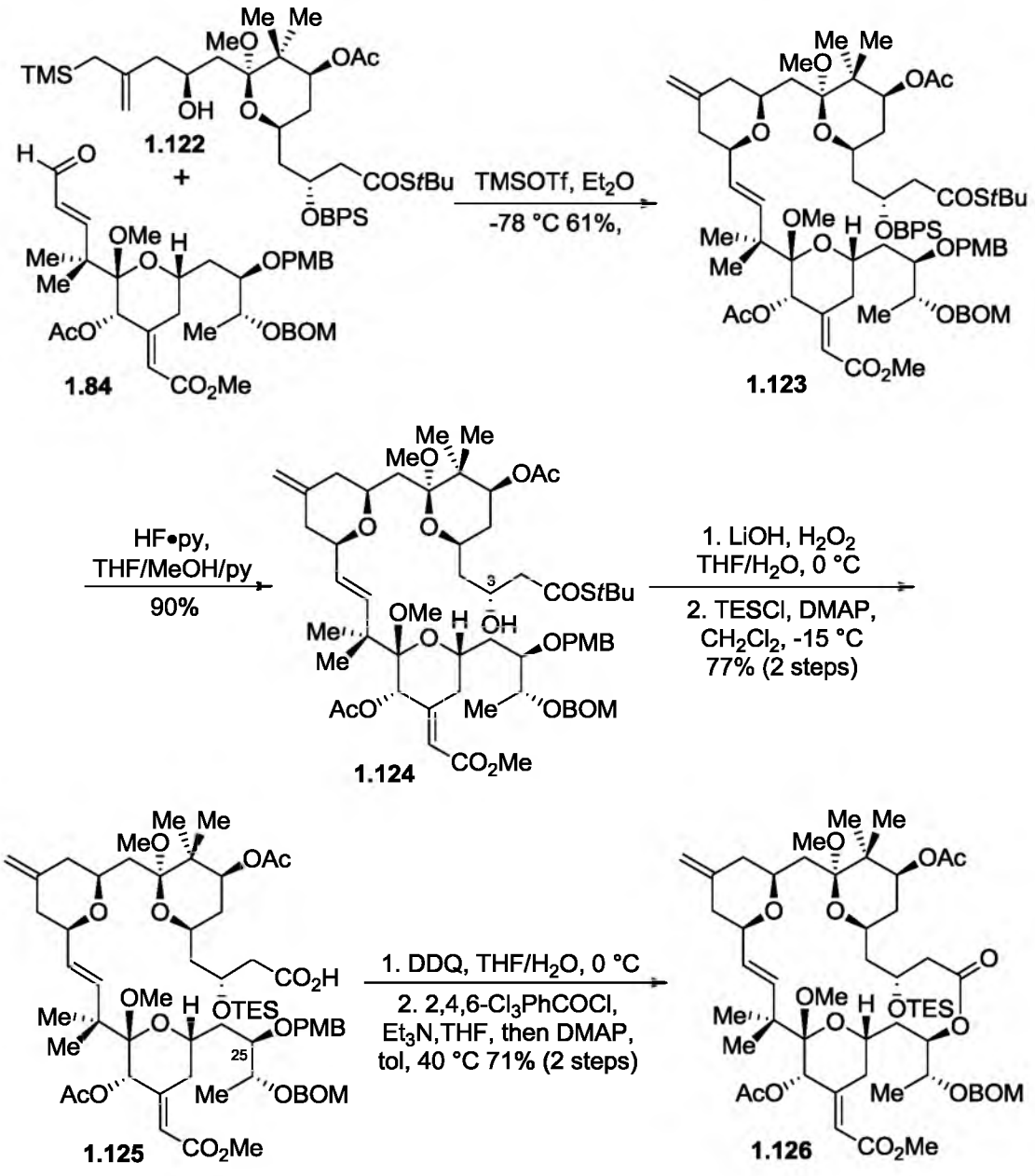


Figure 1.32. Synthesis of Macrolactone **1.126**

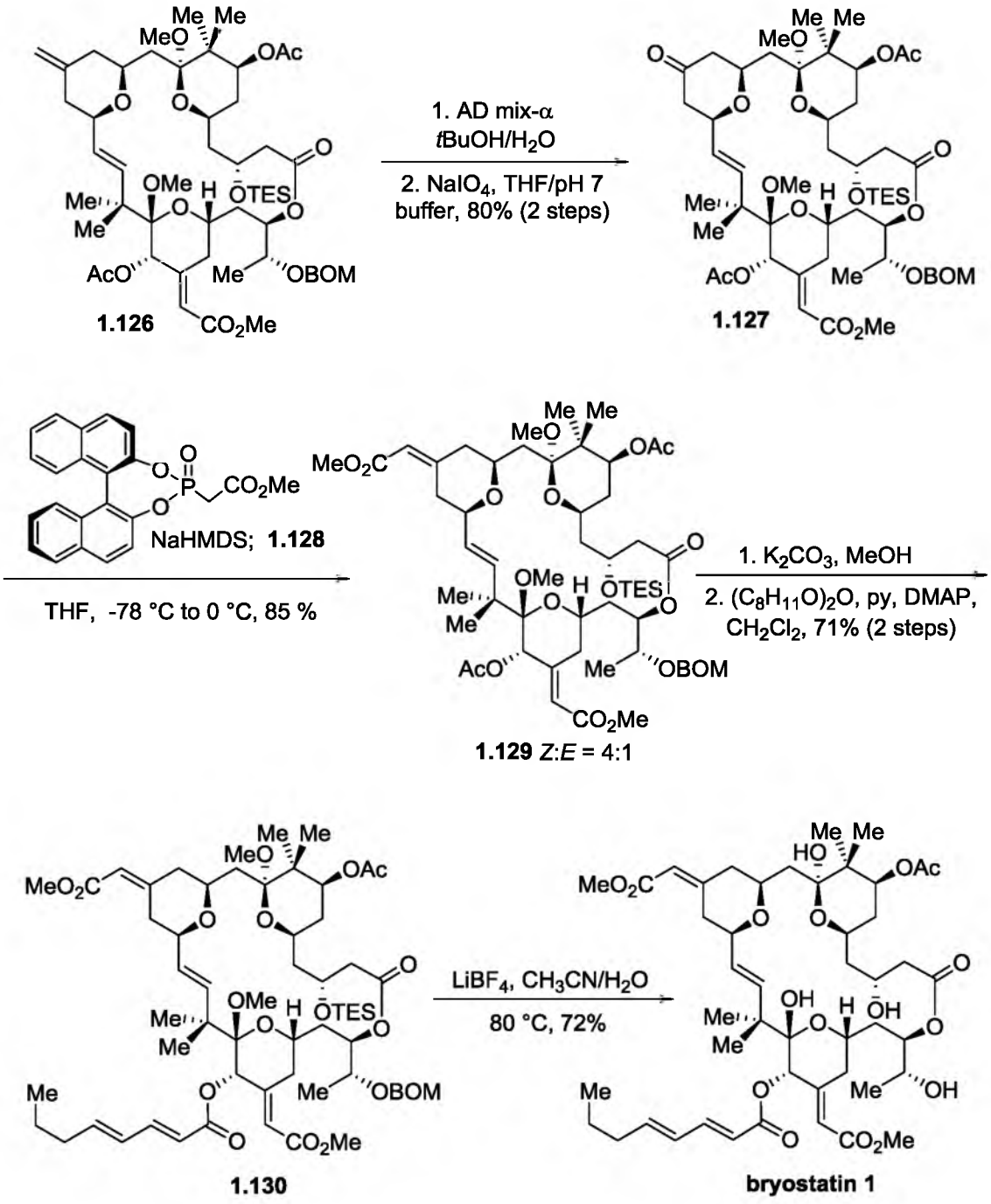


Figure 1.33. Completion of Bryostatin 1

Z:*E* α,β-unsaturated methyl ester **1.129** favoring the desired isomer.[50a] A selective methanolysis of the C20 acetate afforded the C20 alcohol which was then esterified with (2*E*,4*E*)-octa-2,4-dienoic anhydride giving a protected version of bryostatin 1 (**1.130**). Global deprotection using $LiBF_4$ in acetonitrile/H_2O at 80 °C provided bryostatin 1 in 72% yield.

After the publication and the synthesis of bryostatin 1, remaining intermediate **1.127** was used to construct bryostatin 7 (Figure **1.34**). This molecule was simply made by unmasking **1.129** using our global deprotection conditions. The purpose of generating bryostatin 7 was to elucidate it biological profile.

The Biological Profile of Bryostatin 7[78]

An important hypothesis concerning PKC ligands is that the overall lipophilicity of the compounds might play an important role in their biological activity. Prostatin has a phorbol ester backbone, but lacks the hydroxy/acyl group at the C12 carbon. This small difference renders this molecule a nontumor-promoter and a potentially effective

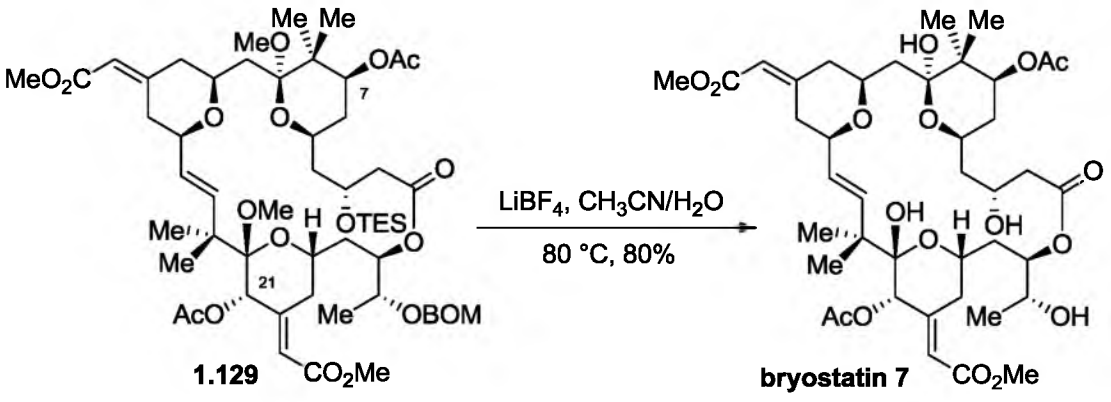


Figure 1.34. Synthesis of Bryostatin 7

HIV therapy.[46a, 82] Interestingly, replacement of prostatin's C13 acetate group with tetradecanoate, a much more lipophilic group, results in a restoration of the molecule's tumor-promoting activity (Figure **1.35**).[83] PEP005 (ingenol 3-angelate) is another example of the drastic effects that lipophilicity can have on biology. This natural product has been FDA approved for actinic keratosis and nonmelanotic skin cancer. It is nontumor-promoting but when the lipophilicity increased, by adding more hydrocarbonto the C3 side chain, the derivatives such as ingenol 3-hexadecanoate turn out to be potent tumor-promoters.[34, 83] The indolactams are another family of natural products that have been identified as potent activators of PKC.[84] So far, this family has shown to be tumor-promoters, but an interesting trend between binding affinity and lipophilicity was observed. One analog of interest is *n*-octyl indolactam V, which binds 20 times better to PKC than indolactam V.

The bryostatins are another class of natural products that bind to PKC, but little is known about the effects of the C20 side chain on biological activity. Comparing bryostatin 1 to bryostatin 7 provides exemplary juxtaposition of lipophilicity at this position to study the biological effects (Figure **1.35**). Bryostatin 7 has the highest binding affinity among the bryostatin family for PKC (mixture of isozymes) with a K_i value of 0.26 nM while bryostatin 1 has a K_i value of 1.35 nM.[85] This is in sharp contrast to that of the indolactams, where additional lipophilicity increases their binding affinity. A detailed biological profile of bryostatin 7 was deemed necessary to determine the significance of the C20 ester side chain.

The following biological studies were conducted by Dr. Blumberg and coworkers at the Natioal Institute of Health (NIH) and are the result of multiple experiments. The

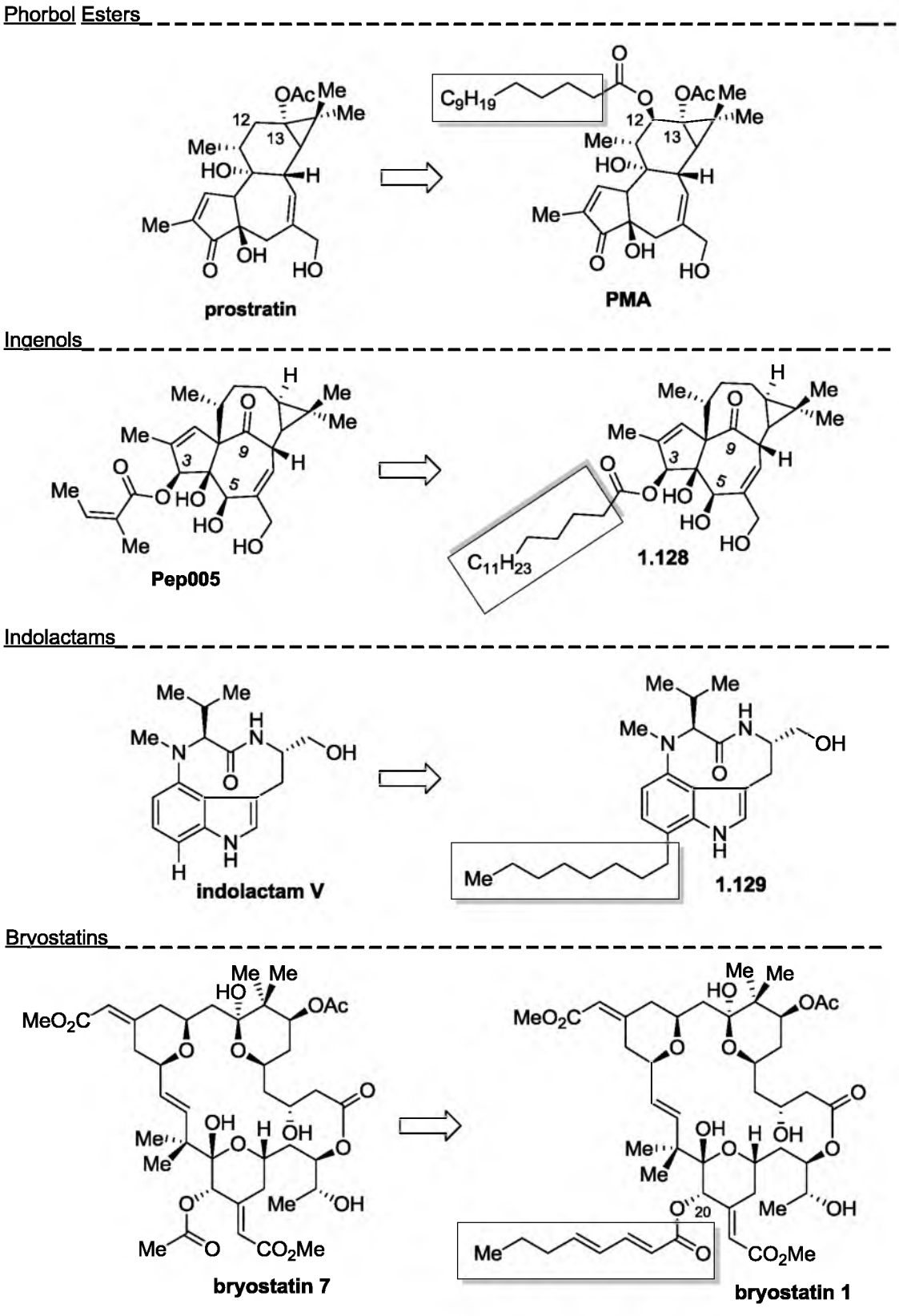


Figure 1.35. Effects of Lipophilic Side Chains

binding affinities of bryostatin 1 and 7 were confirmed. Bryostatin 7 is a stronger binder to PKCα than bryostatin 1, although the difference was slightly less than reported since bryostatin 1's affinity changed from 1.35 nM (mixture of isozymes) to 0.48 nM for PKCα (Table **1.3**).[85] The C1 domain of PKC is highly conserved amongst its isozymes. Experiments were conducted to confirm binding affinities and to evaluate potential isozyme selectivity of bryostatin 1, bryostatin 7, and PMA. Five PKC isozymes were evaluated: PKCα (mouse), PKCα (human), PKCβII, PKCδ, and PKCε. All five isozymes were exposed to various PKC ligands and it was confirmed that there is very little isozyme selectivity or variation in binding affinity with these five isozymes with PKC (Table **1.3**).

Phorbol esters and bryostatin 1 exhibit differential responses in the U937 leukemia cell line. PMA inhibits cell growth and induces cellular attachment, while bryostatin 1 shows a severely reduced response.[86] When bryostatin 1 and PMA are co-administered, the response resembles that of bryostatin 1 alone, showing a dominate mechanism of action. When bryostatin 7 was subjected to the proliferation assay in the U937 cells, it was found

Table 1.3. Binding Affinities of PKC Ligands

	Mouse PKC α	**Human PKC α**	**Human PKCβII**	**Human PKC δ**	**Human PKC ε**
PDBu K_i,nM	0.30 ± 0.05	0.28 ± 0.02	0.20 ± 0.0003	0.33 ± 0.08	0.22 ± 0.05
Bryostatin 1 K_i, nM	0.48 ± 0.03	0.73 ± 0.05	0.42 ± 0.01	0.26 ± 0.02	0.24 ± 0.01
Bryostatin 7, K_i, nM	0.26 ± 0.06	0.44 ± 0.01	0.32 ± 0.01	0.21 ± 0.02	0.16 ± 0.01

to closely resemble bryostatin 1 and was dramatically different from PMA (Figure **1.36**). The biological responses of U937 cells to PMA, bryostatin 1, and bryostatin 7 were measured after a treatment that indicated concentration of ligand for 60 h. Additionally, bryostatin 7 resembled bryostatin 1 by giving a dose-dependent biphasic pattern in its ability to inhibit cell growth. When bryostatin 7 and PMA were co-administered, bryostatin 7 was able to suppress the growth inhibition induced by PMA in a dose-dependent manner. A similar result was obtained in the cell attachment assay. Bryostatin 7, like bryostatin 1, has a reduced level of cell attachment relative to PMA, as well as a dose dependent biphasic response. When co-administered, bryostatin 7 inhibits the attachment induced by PMA. When compared to each other, bryostatin 7 inhibited proliferation slightly more and induced slightly more attachment than bryostatin 1.

Another assay involving U937 cells evaluates the effect of bryostatin 1, bryostatin 7, and PMA on the secretion of tumor necrosis factor α (TNFα). TNFα is an immunomodulating protein produced by immune cells and induces an inflammatory response. It has also been suggested to be an important contributor in PMA's ability to induce apoptosis in U937 cells. After treatment with PMA for 60 h, the ligand induces a very high level of TNFα. Bryostatin 1 and bryostatin 7 induce a similar level of TNFα after treatment , but not as much as PMA (Figure **1.37**).

Since binding affinity and biological response are not correlated for PKC, it is important to evaluate other phenomena such as the ligand's ability to down regulate PKC. Down regulation is caused by binding of the C1 domain, and inducing a conformational change in the protein which ultimately leads to cleavage.[34-35] Bryostatin 1, bryostatin 7, and PMA were evaluated in their ability to effect down regulation of PKCβII, PKCδ, and

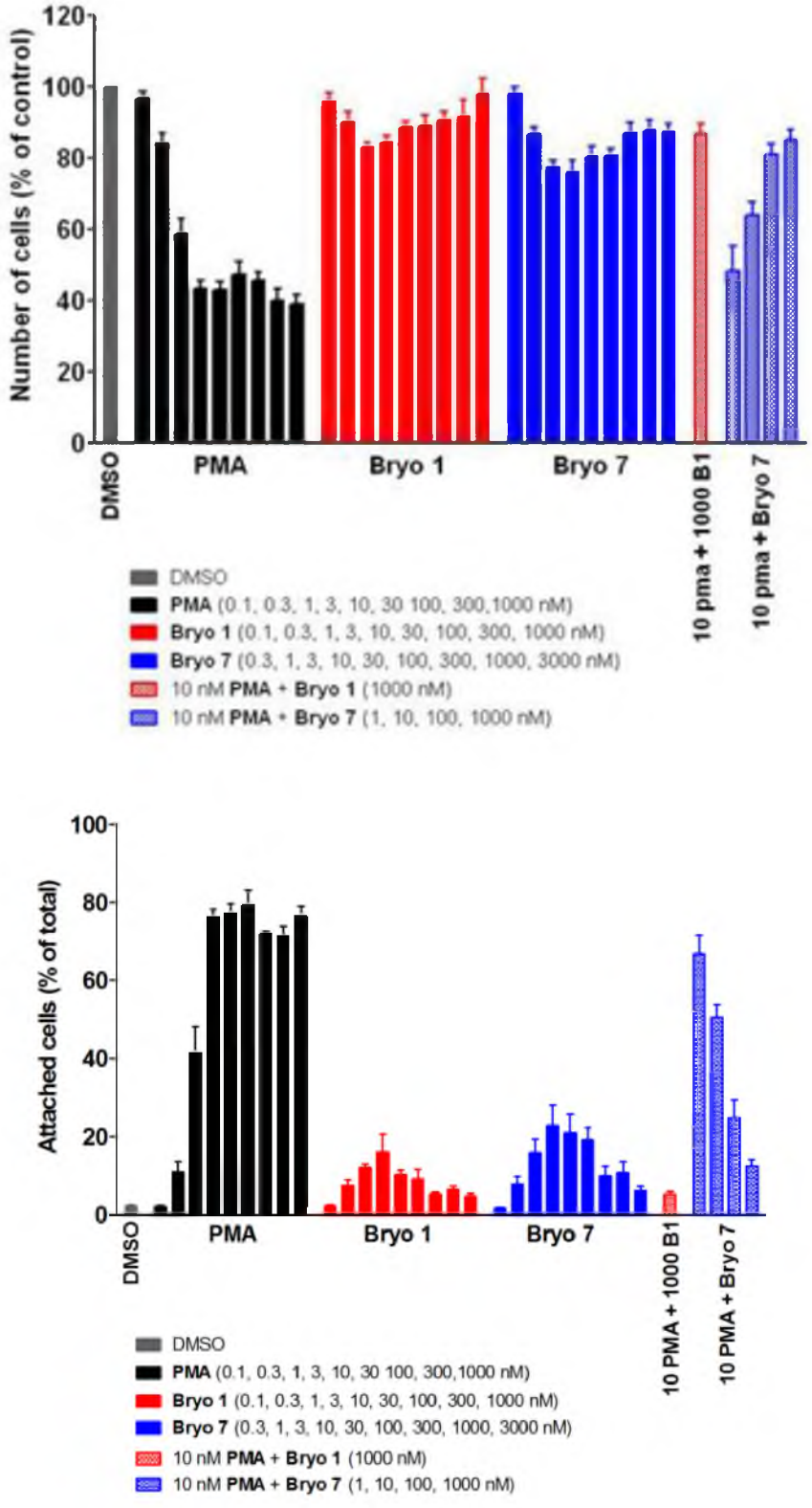


Figure 1.36. Proliferation and Attachment Assay of U937 Cells by Bryostatin 7

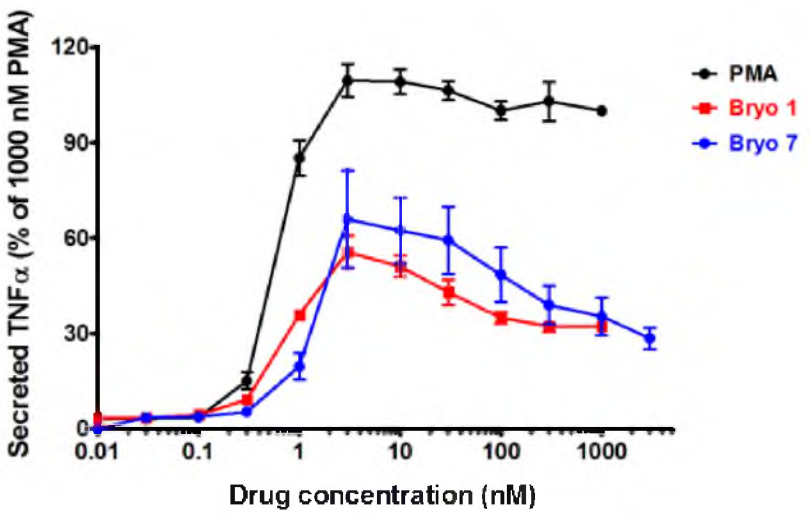


Figure 1.37. TNFα Secretion

PKCε. With PKCε, the bryostatins and PMA showed very little down regulation. In Figure **1.38**, which plots the % of a controlled amount of PKCβII versus ligand concentration, bryostatin 1 (EC_{50} = 0.310 ± 0.005 nM) and bryostatin 7 (EC_{50} =0.97 ± 0.08 nM) induced similar levels of down regulation, while PMA induced less down regulation. With PKCδ, bryostatin 7 had an EC_{50} of 0.22 ± 0.03 nM, while bryostatin 1 was 3 fold more potent with an EC_{50} of 0.083 ± 0.008 nM. PMA is less effective in its ability to down regulate PKCδ while bryostatin 1 and bryostatin 7 give a biphasic dose-dependent response.

In the LNCaP prostate cancer cell line, PMA once again inhibits cellular proliferation, while bryostatin 1 and bryostatin 7 show very little inhibition of cell growth (Figure **1.39**). When bryostatin 1 and 7 are co-administered with PMA, the bryostatins were able to block inhibition of proliferation of PMA. Bryostatin 1 and bryostatin 7 cause a nominal amount of secretion of TNFα and both inhibit the secretion induced by PMA (Figure **1.40**).

The translocation of PKC can be monitored in real time using PKC-green

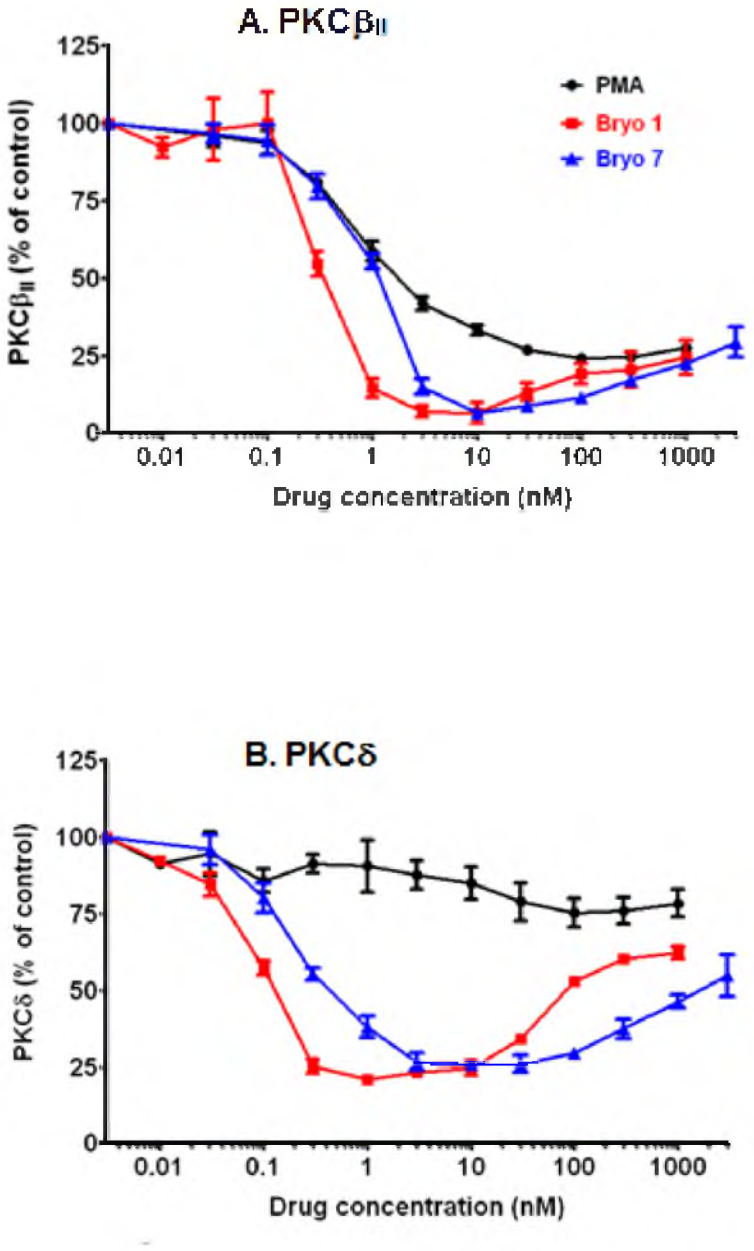


Figure 1.38. Down Regulation of PKCβII and PKCδ in U937 Cells at 24 h

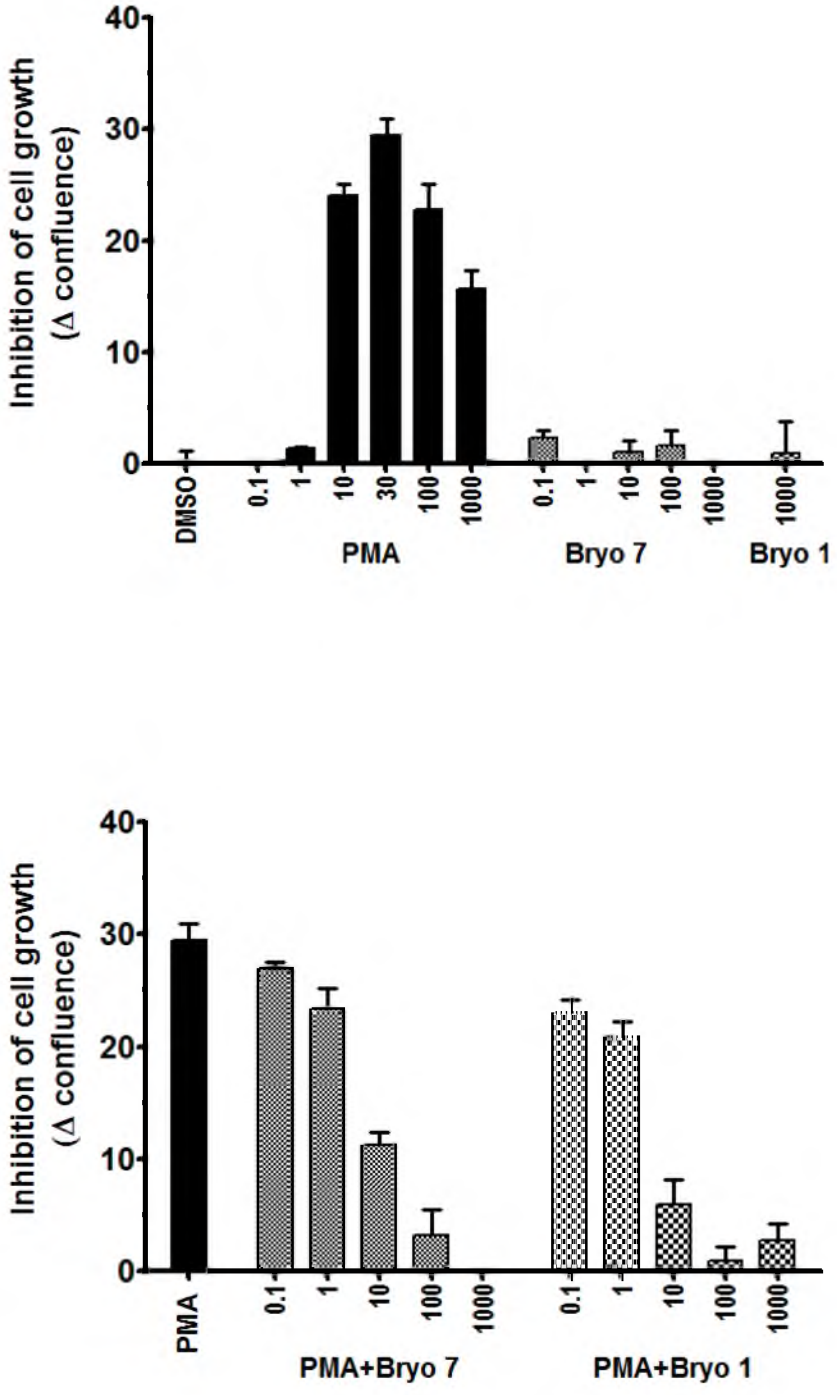


Figure 1.39. Inhibition of Cell Growth in LNCaP Cells

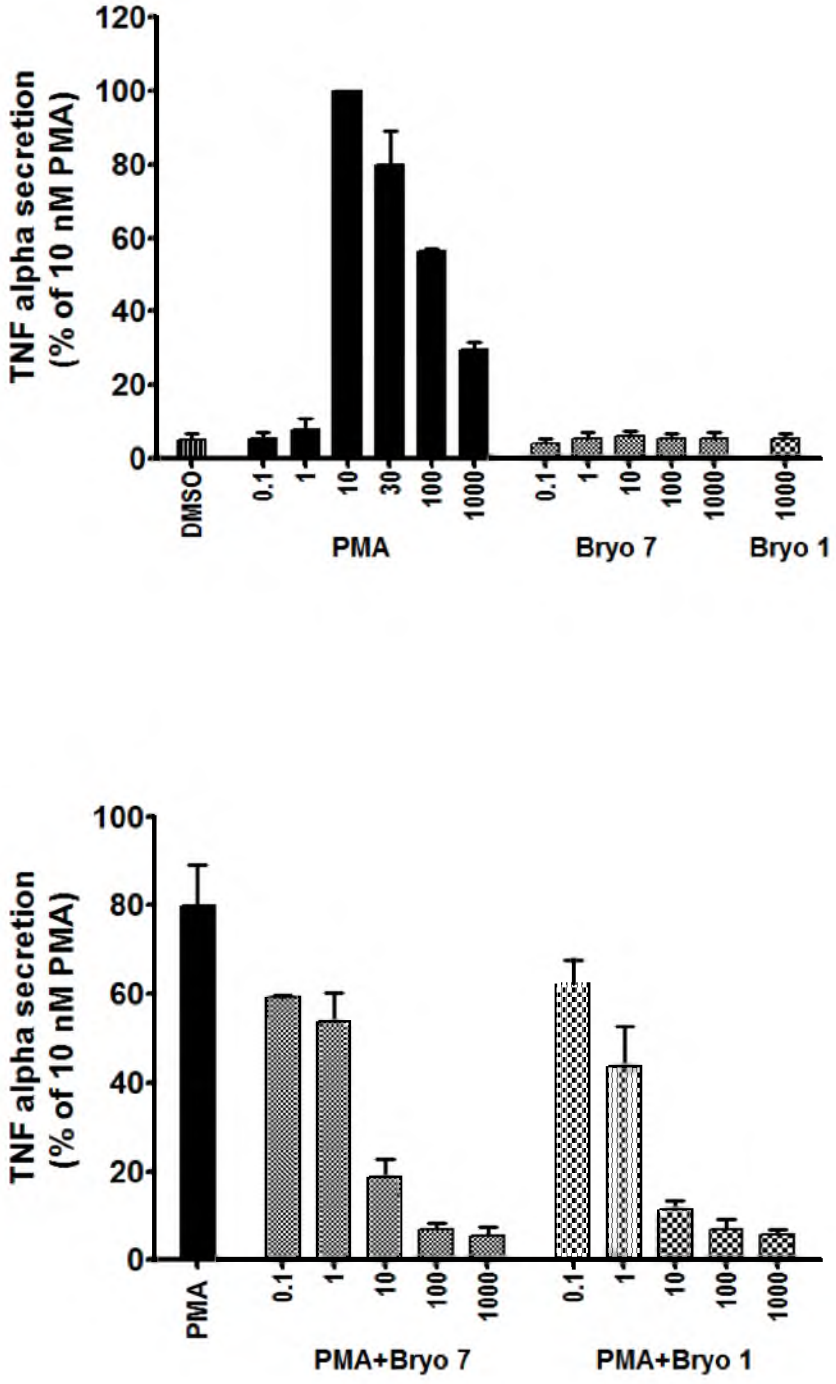


Figure 1.40. TNFα Secretion in LNCaP Cells

fluorescence protein (GFP) conjugates in response to bryostatin 1, bryostatin 7, and PMA. We wanted to evaluate the biological effect that the C20 side chain of bryostatin has on translocation using PKC-GFP. Blumberg and coworkers found that the pattern of translocation of PKCδ varies depending on short, intermediate, or long chained phorbol esters which can be correlated to their tumor-promoting or nontumor-promoting abilities.[87] This indicates that the lipophilicity of the ligands might play a key role in their biological activity. Tumor-promoters such as PMA induce the translocation of PKCδ mostly to the plasma membrane while nontumor-promoters, such as bryostatin 1, cause translocation mainly to the nuclear membrane.[88]

Using mouse PKCδ tagged with GFP and transiently transduced into LNCaP cells, PMA induces translocation of GFP-PKCδ to the plasma membrane while bryostatin 1 induces translocationto the nuclear and internal membranes with minimal plasma membrane translocation (Figure **1.41**). When the GFP mouse PKCδ was exposed to bryostatin 7, there was no visual difference between the translocation patterns seen with bryostatin 1 and bryostatin 7. This was a disappointing result since it was hypothesized that the less lipophilic bryostatin 7 might induce less plasma membrane translocation than bryostatin 1. Using human PKCδ, PMA translocated GFP-PKCδ mostly to the plasma membrane with some translocationto the nuclear and internal membranes (Figure **1.42**). Additionally there is translocation of PKC to the plasma membrane that is substantially less compared to PMA. Interestingly, GFP-PKCδ only translocates to the nuclear and internal membranes by bryostatin 7 with no detectable plasma membrane translocation. This change in translocation correlates to the decrease in lipophilicity of bryostatin 7.

Because there was a difference in the translocation pattern of bryostatin 1 and

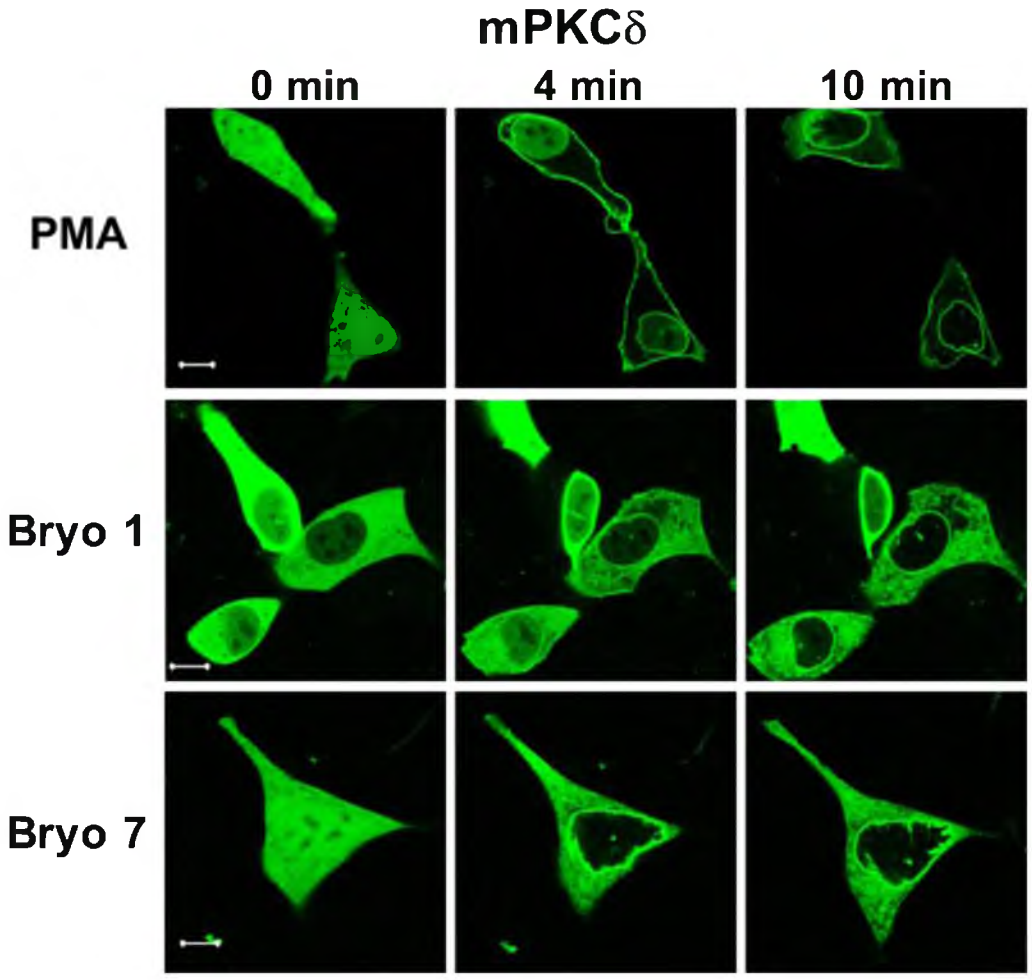


Figure 1.41. Translocation of Mouse GFP-PKCδ in LNCaP Cells

bryostatin 7 with GFP-PKCδ, further examination was warranted. Yellow fluorescence protein (YFP)-PKCε in LNCaP cells were evaluated using confocal microscopy (Figure **1.43**). There was almost exclusive movement of YFP-PKCε to the plasma membrane and swift clearing in the cytoplasm when treated with PMA. Bryostatin 1 retained YFP-PKCε in the cytoplasm, and again resembled PMA in that there is plasma membrane translocation. Bryostatin 7 on the other hand does not induce detectable plasma membrane

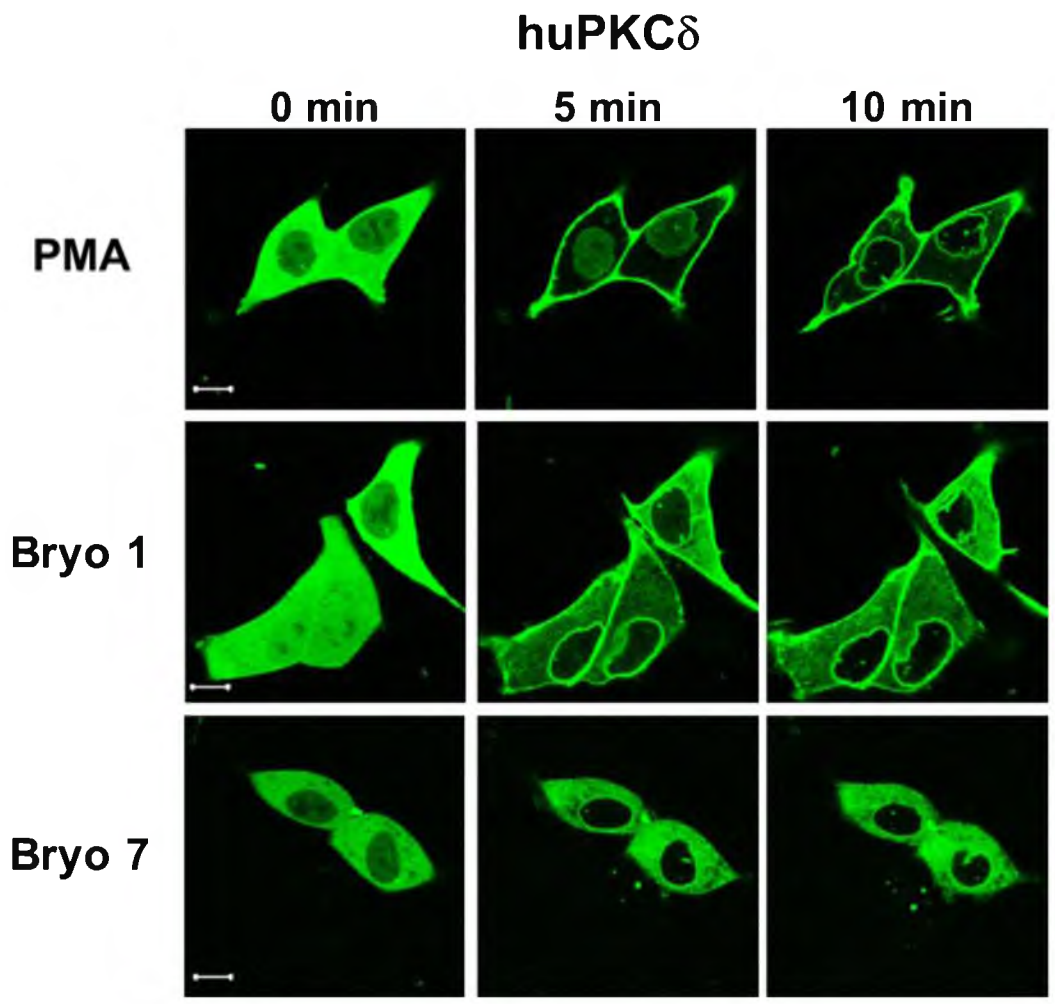


Figure 1.42. Translocation of Human GFP-PKCδ in LNCaP Cells

translocation. Bryostatin 7 on the other hand does not induce detectable plasma membrane translocation and is concentrated in the internal membranes. So far, the results in both GFP-PKCδ and YFP-PKCε are consistent with our original hypothesis that the less lipophilic bryostatin 7 would induce less plasma membrane translocation than bryostatin 1.

The 2 previously examined PKC isozymes, δ and ε, are independent of Ca^{2+} for activation, but are dependent on a C1 domain ligand. An examination of translocation of PKCα, which is an isozyme that is dependent on Ca^{2+}, was evaluated. With mouse PKCα

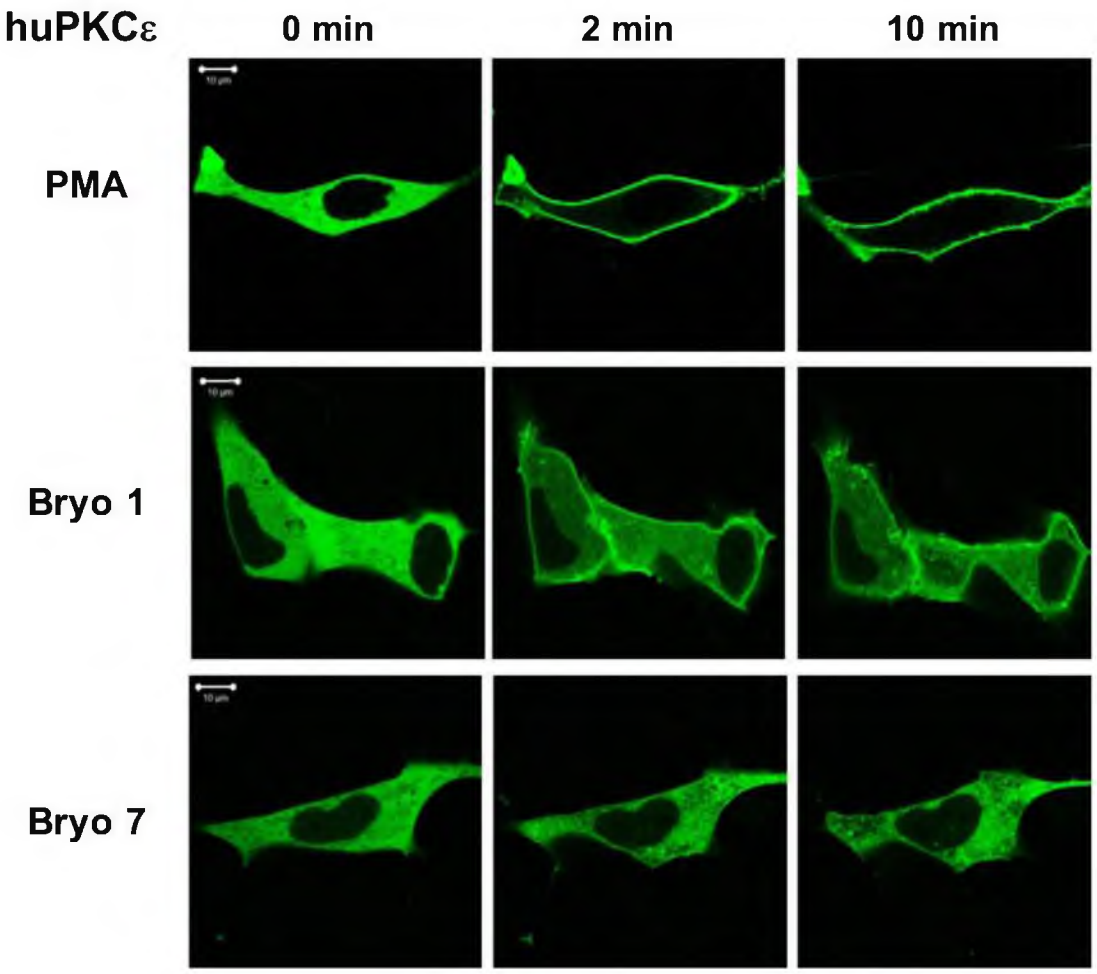


Figure 1.43. Translocation of Human YFP-PKCε in LNCaP Cells

tagged with GFP and transiently transduced into CHO (Chinese hamster ovary) cells, PMA causes translocation of GFP-PKCα to the plasma membrane (Figure **1.44**).[87-88] Bryostatin 1 and bryostatin 7 induce a similar response in these cell lines when looking at translocation of GFP-PKCα. In these cases, there was translocation to the plasma and internal membranes with a high concentration around the nuclear membrane. There was no observed difference between bryostatin 1 and 7 in translocation of PKCα.

Another tool to evaluate the biological profile of PKC effectors is the unique pattern

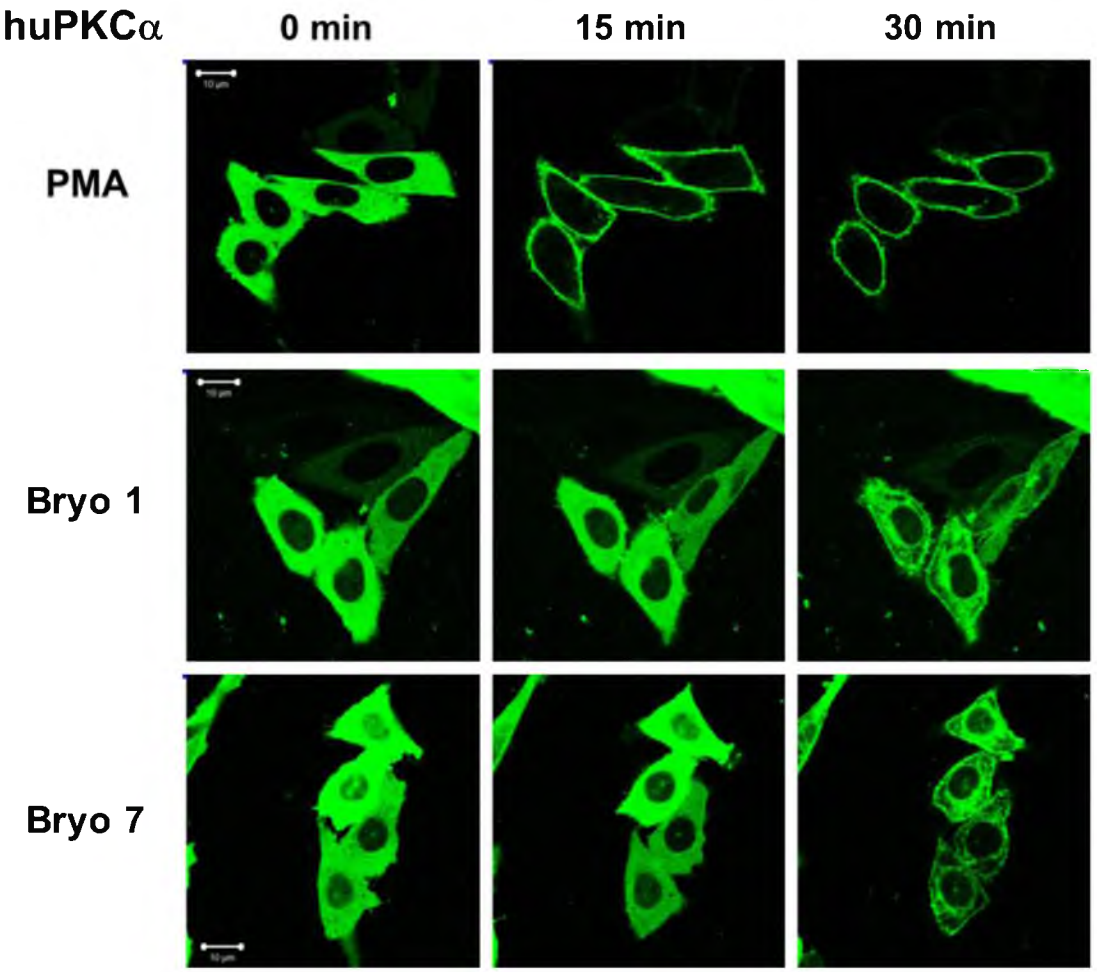


Figure 1.44. Translocation of Human YFP-PKCα in CHO Cells

of gene expression controlled by PKC isozymes. Phorbol esters are known to cause profound changes in gene transcription in LNCaP prostate cancer cells lines.[89] A series of phorbol ester responsive genes were compared to PMA, bryostatin 1, and bryostatin 7 (Figure **1.45**).[89] Changes in levels of mRNA when exposed to PMA were much greater than with bryostatin 1 or bryostatin 7. The levels of mRNA expression for bryostatin 1 and bryostatin 7 resemble one another in this study.

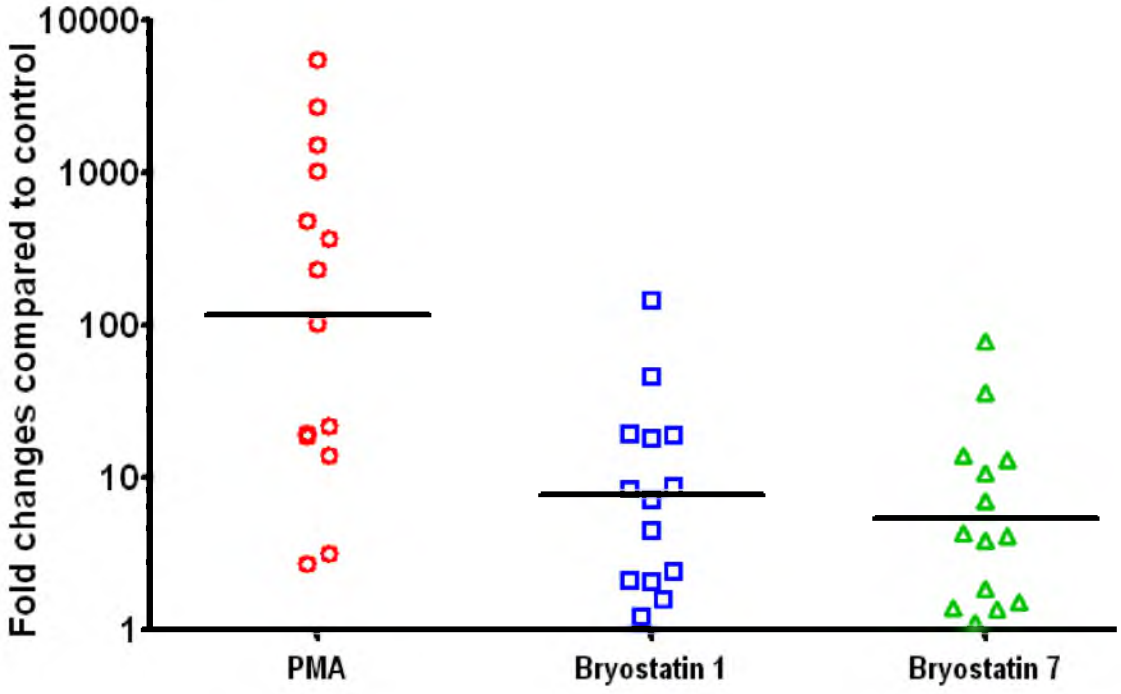


Figure 1.45. Gene Induction in LNCaP Cells

Conclusions

The first total synthesis of bryostatin 1 was accomplished in 30 LLS steps (55 total steps). Bryostatin 7 was determined to retain the biological pattern of bryostatin 1, and is synthetically more accessible using our synthetic route. The less lipophilic bryostatin 7 shows differences in its ability to translocate PKC, but more experiments are required to determine the biological significance of these results in disease models. Overall, the C20 side chain is not a critical element of bryostatin 1 to obtain the biological responses typical of bryostatin 1. The preparation of the C-ring aldehyde **1.84** using a carbonyl/olefin metathesis provided a novel route that produced ample amounts of this fragment and was completed in 18 linear steps. This route provided us a way to incorporate all of the functionality on the C-ring and allowed us to rapidly connect 2 complex pieces using the

pyran annulation. This route was successfully utilized by other members of the group and used to complete synthesis of bryostatin analogs Merle 34-38 shown in Figure **1.46**.

Experimental Section

General Experimental Procedures, Materials, and Instrumentation

Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966).[90] (iPr)$_2$NH, (iPr)$_2$NEt, pyridine, Et_3N, EtOAc, CH_2Cl_2, and TMEDA were distilled from CaH_2. The titer of n-BuLi was determined by the method of Eastham and Watson[91]. Et_2O and THF were distilled from Na under an atmosphere of N_2. MeOH was distilled from dry Mg turnings. $TiCl_4$ was distilled prior to use. Zn was activated with aqueous HCl solution prior to use. Ozone was generated using a Welsbach model T-816 generator. All other reagents were used without further purification. Yields were calculated for material judged homogenous by thin layer chromatography and nuclear magnetic resonance (NMR). Thin layer chromatography was performed on Merck Kieselgel 60 Å F_{254} plates or Silicycle 60Å F_{254} eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid, 4-anisaldehyde, or an aqueous potassium permanganate solution. Flash column chromatography was performed with Silicycle flash silica gel 40 – 63 μm, slurry packed with hexanes in glass columns. Glassware for reactions was oven dried at 125 °C and cooled under a dry nitrogen atmosphere prior to use. Liquid reagents and solvents were introduced by oven dried syringes through septum-sealed flasks under a nitrogen atmosphere. Nuclear magnetic resonance spectra were acquired at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts

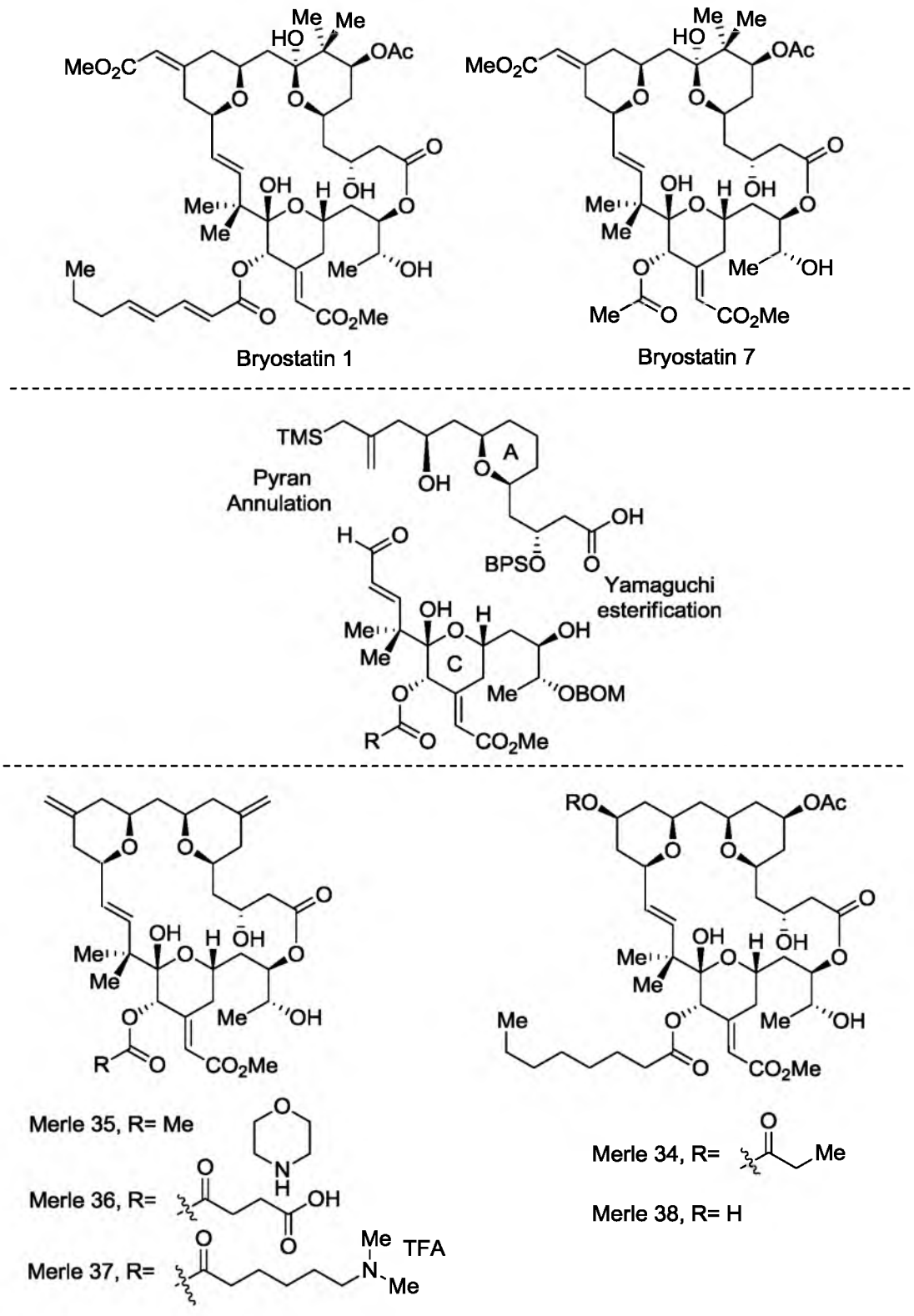


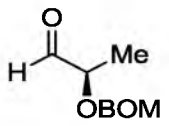
Figure 1.46. Uses of the C-ring Subunit

for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million relative to the signal residual $CDCl_3$ at 7.27 ppm. Chemicals shifts for carbon nuclear magnetic resonance (^{13}C NMR and DEPT) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.23 ppm. Chemical shifts of the unprotonated carbons ('C') for DEPT spectra were obtained by comparison with the ^{13}C NMR spectrum. The abbreviations s, d, apd, dd, ddd, dddd, t, td, tt, q, dq, and m stand for the resonance multiplicity singlet; doublet; apparent doublet; doublet of doublets; doublet of doublet of doublets; doublet of doublet of doublet of doublets; doublet of doublet of doublets of doublets; triplet; triplet of doublets; triplet of triplets; quartet; doublet of quartets; and multiplet, respectively. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length. Specific rotations ($[\alpha]_D^{20}$, Unit: °cm^2/g) are based on the equation $\alpha = (100 \cdot \alpha)/(l \cdot c)$ and are reported as unitless numbers where the concentration c is in g/100 mL and the path length l is in decimeters. Mass spectrometry was performed at the mass spectrometry facility of the Department of Chemistry at The University of Utah on a double focusing high resolution mass spectrometer. Compounds were named using ChemDraw 12.0.0.

Experimental Procedures and Analytical Data for Homoallylic Alcohol **1.67**

Compounds **1.64-1.67** were previously prepared by Dr. Anh Truong and are reported in her Ph.D. thesis[92] and in the literature.[65] These syntheses were repeated on a larger scale in order to access for use in the present work. A larger scale experimental

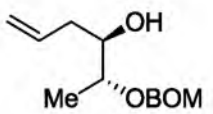
procedure and analytical data for these compounds are reproduced here, for those who may need to repeat this work.



(*R*)-2-((benzyloxy)methoxy) propanal (1.64).[65] To a stirring solution of (*R*)-(+)-isobutyl lactate (24.0 mL, 160.1 mmol, 1.0 equiv) and (iPr)$_2$NEt (84.0 mL, 480.0 mmol, 3.0 equiv) at 0° C in a 250 ml rb flask, was added benzyl chloromethylether (44.5 mL, 320.0 mmol, 2.0 equiv) via syringe. The solution was stirred overnight during which it slowly returned to rt. The reaction mixture was quenched by the addition of aqueous HCl solution (50 mL of 1.0 M) and diluted with Et_2O (200 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 200 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude ester. Purification was accomplished by flash column chromatography using an 10.0 × 19.0 cm silica gel column, eluting with 10% EtOAc/ hexanes, collecting 125 mL Erlenmeyer flask fractions. The product containing fractions (8-45) was concentrated under reduced pressure to yield impure ester as a clear colorless oil.

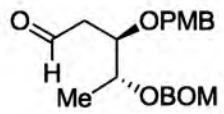
To a stirring solution of impure ester in CH_2Cl_2 (450 mL) in a 1 L rb flask at -78° C, was added DIBAL-H (1.0 M in CH_2Cl_2, 112.4 mL, 112.4 mmol, 1.2 equiv) via syringe pump at a rate of 22.4 mL/hr. The reaction was allowed to proceed for 1 h at -78 °C, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched with MeOH (50 mL) added via syringe pump at a rate of

25 mL/hr. The reaction mixture was poured into a stirring saturated aqueous solution of sodium potassium tartrate (500 mL) and stirred at rt overnight. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (500 mL × 2). The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The aldehyde was purified by flash column chromatography using an 8.0 × 10.0 cm silica gel column, eluting with 15% EtOAc/ hexanes, collecting 125 mL Erlenmeyer flask fractions. The product containing fractions (8-38) was concentrated under reduced pressure to yield pure aldehyde **1.64** (24.2 g, 78%, 2 steps) as a colorless oil: R_f = 0.51 (30 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.65 (d, *J* = 1.6 Hz, 1H), 7.41-7.28 (m, 5H), 4.88 (s, 2 H), 4.71 (d, *J*= 11.8 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.12 (dq, *J* = 7.0, 1.5 Hz, 1H), 1.34 (d, J = 7.1, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 202.5, 137.4, 128.6, 127.9, 127.8, 94.2, 78.2, 70.0, 15.3.



(2*R*,3*R*)-2-((benzyloxy)methoxy)hex-5-en-3-ol (1.65).[65] To a stirring solution of aldehyde **1.64** (13.7 g, 70.6 mmol, 1.0 equiv) in CH_2Cl_2 (600 mL) in a 1 L rb flask, was added $MgBr_2$•Et_2O (36.6 g, 141.3 mmol, 2.0 equiv). The solution was stirred at rt for 5 min and then cooled to -15° C. Stirring continued for 15 min, and a solution of allyltributyltin (33.0 mL, 106.0 mmol, 1.5 equiv) in CH_2Cl_2 (80 mL) was added to the reaction mixture over 20 min via cannula. The solution was allowed to reach rt as stirring continued overnight. The reaction mixture was quenched by pouring the mixture into a 2 L Erlenmeyer flask containing saturated aqueous $NaHCO_3$ solution (250 mL), aqueous KF

solution (250 mL), and CH_2Cl_2 (250 mL). The mixture stirred at rt for 2 h and the phases were then separated. The aqueous phase was extracted with CH_2Cl_2 (300 mL × 3). The combined organic phases were washed with aqueous saturated brine solution (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography using a 10.0 × 14.0 cm silica gel column, eluting with 2-25% EtOAc/ hexanes, collecting 125 mL Erlenmeyer flask fractions. The product containing fractions (15-25) was concentrated under reduced pressure to yield homoallylic alcohol **1.65** (13.5 g, 81%) as a clear colorless oil: R_f = 0.40 (30 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.29 (m, 5H), 5.91 (dddd, *J* = 16.6, 9.8, 7.3, 6.3 Hz, 1H), 5.18-5.10 (m, 2H), 4.88 (d, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 3.68 (dq, *J* = 6.4, 6.4 Hz, 1H), 3.56 (dddd, *J* = 7.9, 5.9, 3.9, 3.9 Hz, 1H), 2.61 (d, *J* = 3.9 Hz, 1H), 2.41-2.34 (m, 1H), 2.27-2.20 (m, 1H), 1.23 (d, *J* =6.4 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 137.7, 134.9, 128.7, 128.1, 128.0, 117.7, 94.1, 77.3, 74.4, 70.0, 37.8, 16.9.



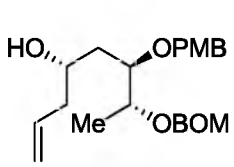
(3*R*,4*R*)-4-((benzyloxy)methoxy)-3-((4-methoxy benzyl) oxy)pentanal (1.66).[65]

To a stirring solution of KH (35% in mineral oil, 10.5 g, 91.5 mmol, 1.5 equiv) in THF (500 mL) in a 1L rb flask at 0° C, was added a solution of homoallylic alcohol **1.65** (14.4 g, 61.0 mmol, 1.0 equiv) in THF (80 mL) dropwise via cannula. The flask was rinsed with an additional THF (10 mL) and slowly added to the reaction mixture. This was repeated 2 more times. The mixture was stirred at 0° C for 5 min, and then PMB-Br (13.2 mL, 91.5

mmol, 1.5 equiv) was added dropwise via syringe. The reaction was allowed to proceed for 2 h at 0 °C, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by adding a saturated aqueous solution of NH_4Cl (200 mL). The mixture was diluted with Et_2O (300 mL) and H_2O (100 mL) was added. The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 300 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 15.0 cm silica gel column, eluting with 20% EtOAc/ hexanes, collecting 125 mL Erlenmeyer flask fractions. The product containing fractions (9-19) were combined and concentrated under reduced pressure to yield crude PMB ether as a clear oil with inseparable impurities.

To a stirring solution of impure alkene in CH_2Cl_2/ MeOH (4:1, 600 mL), was added $NaHCO_3$ (51.3 g, 610.2 mmol, 10.0 equiv). The reaction mixture was cooled to -78° C and O_3 was bubbled through the mixture until the solution developed a light blue color. The excess O_3 was purged from the reaction mixture by bubbling O_2 through it for 20 min. Dimethyl sulfide (44 ml, 598.0 mmol, 9.8 equiv) was added to the mixture dropwise via syringe. The solution was slowly allowed to reach rt overnight. The solid $NaHCO_3$ was removed by filtration, and the solution was concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 15.0 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 125 mL Erlenmeyer flask fractions. The product containing fractions (13-30) were combined and concentrated under reduced pressure to yield aldehyde **1.66** (19.9 g, 96%) as clear colorless oil: $R_f = 0.40$ (30 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.74 (dd, J = 2.2, 1.3 Hz, 1H), 7.43-7.17

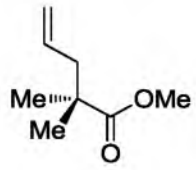
(m, 7H), 6.89-6.84 (m, 2H), 4.82 (d, J = 7.3 Hz, 1H), 4.77 (d, J = 7.0 Hz, 1H), 4.60 (s, 2H), 4.55 (d, J = 11.3 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 4.08-3.96 (m, 2H), 3.80 (s, 3H), 2.67 (ddd, J = 4.3, 1.1, 1.1 Hz, 1H), 2.64 (ddd, J = 7.7, 2.4, 0.9 Hz, 1H), 1.21 (d, J = 6.5 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 201.5, 159.5, 137.9, 130.2, 129.8, 128.7, 128.0, 128.0, 114.0, 93.7, 75.6, 73.1, 72.3, 69.9, 55.4, 44.4, 15.1.



(4*S*,6*R*,7*R*)-7-((benzyloxy)methoxy)-6-((4-methoxy benzyl)oxy)oct-1-en-4-ol (1.67).[65] To a stirring solution of aldehyde **1.66** (19.7 g, 60.0 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) in a 1 L rb flask, was added $MgBr_2 \bullet Et_2O$ (28.4 g, 109.9 mmol, 2.0 equiv). The solution was stirred at rt for 5 min, and was then cooled to -15 °C where stirring continued for an additional 25 min. A solution of allyltributyltin (25.5 mL, 82.4 mmol, 1.5 equiv) in CH_2Cl_2 (50 mL) was added to the reaction mixture via cannula over a 30 min. The reaction was allowed to proceed for 60 h at -15 °C, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by pouring the mixture into a 2 L Erlenmeyer flask containing a stirring solution of saturated aqueous $NaHCO_3$ solution (150 mL) and aqueous KF solution (150 mL). The mixture was stirred for 3 h at room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (400 mL × 3). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 12.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 250 mL Erlenmeyer flask fractions. The product

containing fractions (7-22) were combined and concentrated under reduced pressure to yield homoallylic alcohol **1.67** (21.2 g, 96%) as clear colorless oil, and as a 7:1 mixture of diastereomers as determined by ^{1}H and ^{13}C NMR: R_f = 0.29 (30 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (m, 7H), 6.89-6.83 (m, 2H), 5.82 (dddd, *J* = 16.6, 9.8, 6.8, 6.8 Hz, 1H), 5.14-5.06 (m, 2H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.61 (s, 2H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 10.9 Hz, 1H), 4.01 (dq, *J* = 6.3, 5.9 Hz, 1H), 3.88-3.82 (m, 1H), 3.81 (s, 3H), 3.77-3.70 (m, 1H), 2.28 (d, *J* = 4.4 Hz, 1H), 2.25-2.18 (m, 2H), 1.68-1.64 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 159.5, 138.1, 135.1, 130.7, 129.8, 128.7, 128.0, 127.9, 118.0, 114.0, 93.9, 78.4, 74.0, 72.7, 69.8, 67.9, 55.5, 42.6, 36.6, 15.6.

Experimental Procedures and Analytical Data for Fully Functionalized C-ring **1.103**

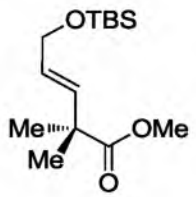


Methyl 2,2-dimethylpent-4-enoate (1.91).[65] To a stirring solution of (iPr)$_2$NH (36.7 mL, 260 mmol, 1.1 equiv) in THF (160 mL) in a 1 L rb flask at -78 °C, was added *n*-BuLi (2.6 M in hexanes, 100 mL, 260 mmol, 1.1 mmol). The solution was stirred at -78 °C for 30 min and was then allowed to warm to 0 °C for 30 min. Methyl isobutyrate (30 mL, 236 mmol, 1.0 equiv) in THF (100 mL) in a 250 ml rb flask, was added slowly via cannula over 30 min down the side of the flask to the resulting solution of LDA at -78 °C. An additional THF rinse (20 mL) was used to transfer remaining residue into the reaction flask via cannula. The resulting light-yellow reaction mixture was allowed to stir at -78 °C

for 1 h and allyl bromide (24.0 mL, 260 mmol, 1.1 equiv) in THF (140 mL) was added slowly via cannula down the side of the flask. The reaction mixture stirred at -78 ºC for 30 min and was allowed to warm to rt. This solution was stirred for 2 h, then quenched by the addition of saturated aqueous NH_4Cl solution (150 mL) and diluted with pentane (500 mL). The phases were separated and the organic phase was washed with a saturated aqueous $Na_2S_2O_3$ solution (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished using fractional distillation, collecting at 125 ºC – 145 ºC to yield olefin **1.91** (25 mL, 74%) as a colorless liquid: R_f = 0.40 (5 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.78-5.68 (m, 1H), 5.07-5.06 (m,1H), 5.05-5.02 (m, 1H), 3.67 (s, 3H), 2.28 (dt, *J* = 7.8, 1.0 Hz, 2H), 1.18 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 178.1, 134.4, 118.0, 51.8, 44.9, 42.5, 25.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.8, 25.0; CH_2 δ 118.0, 44.9; CH_1 δ 134.4; CH_0 δ 178.1, 42.5; IR (neat) 2960, 2925, 2872, 1731, 1469, 1384, 1147 995, 914 cm^{-1}; HRMS (ESI) calcd for $C_8H_{15}O_2$(M+H): 143.1072, found: 143.1068.

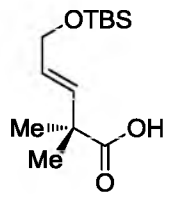
(*E*)-methyl 5-bromo-2,2-dimethylpent-3-enoate (1.92). To a stirring solution of olefin **1.91** (12.0 g, 84.3 mmol, 1.0 equiv) in CCl_4 (85 mL, 1.0 M) in a 250 ml rb flask, was added *N*-bromosuccidimide (16.5 g, 92.8 mmol, 1.1 equiv) followed by benzoyl peroxide (70% in H_2O, 0.6 g, 1.7 mmol, 0.02 equiv). This solution was heated at reflux for 2 h and

cooled to rt. An additional portion of *N*-bromosuccidimide (7.5 g, 42.2 mmol, 0.5 equiv) was added and the solution was again heated at reflux for 2 h. After cooling to rt, the solution was filtered with the aid of CH_2Cl_2 and the filtrate was concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 14.0 cm silica gel column, eluting with 5% EtOAc/ hexanes, collecting 125 mL fractions. The product containing fractions (8-26) were combined and concentrated under reduced pressure to yield bromide **1.92** (13.1 g, 70%) as a clear yellow oil: R_f = 0.44 (5% EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.97 (dt, *J* = 15.7, 1.0 Hz, 1H), 5.74 (dt, *J* = 15.6, 7.3 Hz, 1H), 3.97 (dd, *J* = 7.3, 1.0 Hz, 2H), 3.69 (s, 3H), 1.32 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ176.4, 139.6, 125.0, 52.4, 44.3, 32.9, 25.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 52.4, 25.0; CH_2 δ 32.9; CH_1 δ 139.5, 125.0; CH_0 δ 176.4, 44.3; IR (neat) 2978, 2951, 2875, 1731, 1469, 1432, 1262, 1145, 969 cm^{-1}; HRMS (ESI) calcd for $C_8H_{13}NaO_2Br$ (M+Na): 242.9997, found: 243.0014.



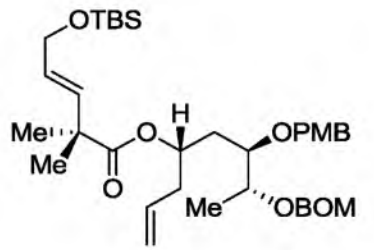
(*E*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl pent-3-enoate (1.93). To a stirring solution of 2,6-di-*tert*-butyl-4-methylpyridine (17.7 g, 86.6 mmol, 1.5 equiv) in CH_2Cl_2 (120 mL) in a 500 ml rb flask at 0° C, was added silver triflate (17.8 g, 69.3 mmol, 1.2 equiv) followed by TBSOH (13.6 mL, 86.6 mmol, 1.5 equiv). Stirring continued for 5 min, and a solution of allylbromide **1.92** (12.8 g, 57.7 mmol, 1.0 equiv), in CH_2Cl_2 (50 mL) was added to the reaction mixture over 20 min via cannula. An additional CH_2Cl_2

rinse (10 mL) was used to transfer the remaining residue into the reaction flask via cannula. After stirring at 0° C for 30 min, the precipitate of AgBr solid was filtered off and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, then purified by flash column chromatography using a 10.0 × 12 cm silica gel column, eluting with 10% EtOAc/ hexanes, collecting 125 mL fractions. The product containing fractions (4-11) were combined and concentrated under reduced pressure to yield TBS ether **1.93** (13.3 g, 84%) as a clear yellow oil: R_f = 0.62 (10 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.84 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.59 (dt, *J* = 15.6, 4.3 Hz, 1H), 4.18 (dd, *J* = 4.3, 1.5 Hz, 2H), 3.68 (s, 3H), 1.31 (s, 6H), 0.91 (s, 9H), 0.07 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 177.0, 134.7, 127.9, 63.9, 52.1, 44.0, 26.1, 25.1, 18.6, -5.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 52.1, 26.1, 25.1, -5.0; CH_2 δ 63.9; CH_1 δ 134.7, 127.9; CH_0 δ 177.0, 44.6, 18.6; IR (neat) 2955, 2931, 2857, 1732, 1471, 1256, 1141, 837, 776 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{28}NaO_3Si$ (M+Na): 295.1705, found: 295.1709.



(E)-5-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpent-3-enoic acid (1.88). To a stirring solution of ester **1.93** (16.8 g, 61.5 mmol, 1.0 equiv) in 3:1 EtOH/H_2O (200 mL, 0.3 M) in a 500 ml rb flask at 0° C, was added sodium hydroxide (12.3 g, 307 mmol, 5.0 equiv). The reaction was allowed to proceed for 15 h at 5° C, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by transfer into a 1 L separatory funnel that contained a mixture of a EtOAc (300

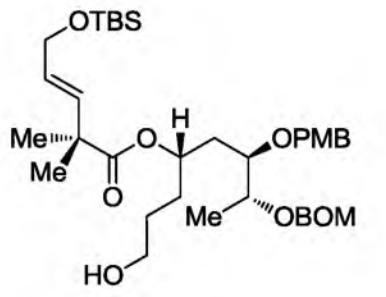
mL) and pH 2 aqueous buffer (300 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 300 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 10.0 cm silica gel column, eluting with 15% EtOAc/ hexanes, collecting 125 mL fractions. The product containing fractions (5-16) were combined and concentrated under reduced pressure to yield acid **1.88** (15.3 g, 93%) as a clear yellow oil: R_f = 0.54 (50 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.87 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.65 (dt, *J* = 15.6, 4.9 Hz, 1H), 4.20 (dd, *J* = 4.9, 1.5 Hz, 1H), 1.34 (s, 6H), 0.91 (s, 9H), 0.07 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 183.2, 134.2, 128.4, 63.9, 43.9, 26.1, 25.1, 24.9, 18.6, -5.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 26.1, 24.9, -5.0; CH_2 δ 63.9; CH_1 δ 134.2, 128.4; CH_0 δ 183.2, 43.9, 18.6; IR (neat) 2955, 2930, 2858, 1705, 1472, 1255, 1104, 837, 777 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{26}NaO_3Si$ (M+Na): 281.1549, found: 281.1540.



(*E*)-(4*S*,6*R*,7*R*)-7-((benzyloxy)methoxy)-6-((4-methoxybenzyl)oxy)oct-1-en-4-yl 5-((*tert*-butyldimethylsilyl)oxy) -2,2-dimethyl pent-3-enoate (1.98). To a stirring solution of alcohol **1.67** (17.2 g, 42.8 mmol, 1.0 equiv) and acid **1.88** (14.0 g, 53.0 mmol, 1.2 equiv) in CH_2Cl_2 (40 mL) in a 250 ml rb flask at 0° C, was added DMAP (7.9 g, 64.3 mmol, 1.5 equiv), DMAP▪HCl (6.8 g, 42.8 mmol, 1.0 equiv) followed by 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (20.0 g, 128.5 mmol, 3.0 equiv). The reaction was

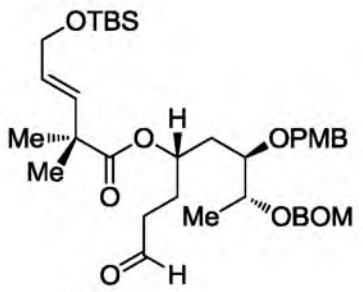
allowed to proceed for 15 h at rt, after which time TLC analysis indicated complete consumption of the alcohol starting material. The reaction mixture was quenched by transfer into a 2 L separatory funnel that contained a mixture of a 20% EtOAc/Hex (400 mL) and H_2O (300 mL). The phases were separated, and the aqueous phase was extracted with 20% EtOAc/Hex (2 × 400 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 12.0 cm silica gel column, eluting with 10% EtOAc/ hexanes, collecting 125 mL fractions. The product containing fractions (20-77) were combined and concentrated under reduced pressure to yield ester **1.98** (23.9 g, 87%) as a clear yellow oil: $R_f = 0.47$ (30 % EtOAc/Hex.); $[\alpha]_D^{20} = +30.8$ ($c = 1.0$, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.25 (m, 7H), 6.88-6.84 (m, 2H), 5.86 (ddd, J = 16.2, 2.0, 2.0 Hz, 1H), 5.79 (dddd, J = 17.1, 9.8, 6.8, 6.8 Hz, 1H), 5.75 (ddd, J = 21.0, 5.4, 5.4 Hz, 1H), 5.21 (dddd, J = 6.7, 6.7, 6.7, 3.3 Hz, 1H), 5.07-5.04 (m, 1H), 5.04-5.25 (m, 1H), 4.82 (d, J = 6.8 Hz, 1H), 4.78 (d, J = 6.8 Hz, 1H), 4.62 (ddd, J = 11.7, 11.7, 11.7 Hz, 2H), 4.52 (d, J = 10.8 Hz, 1H), 4.36 (d, J = 10.8 Hz, 1H), 4.16 (dd, J = 4.9, 1.5 Hz, 2H), 3.95 (dq, J = 6.8, 6.4 Hz, 1H), 3.79 (s, 3H), 3.43 (ddd, J = 10.3, 4.9, 2.0 Hz, 1H), 2.40-2.26 (m, 1H), 1.84-1.77 (m, 1H), 1.70-1.62 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H), 1.18 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 175.9, 159.4, 138.0, 134.7, 133.6, 130.6, 129.9, 128.6, 128.1, 128.0, 127.9, 127.8, 118.0, 114.0, 93.4, 77.4, 73.2, 73.1, 70.4, 69.5, 63.9, 55.4, 44.1, 39.6, 34.4, 26.1, 25.3, 25.1, 15.3, -4.9; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 26.1, 25.3, 25.1, 15.4, -4.9; CH_2 δ 118.0, 93.4, 73.1, 69.5, 64.0, 39.6, 34.5; CH_1 δ 134.7, 133.6, 129.9, 128.6, 128.0, 127.9, 127.8, 113.9, 77.4, 73.4, 70.4; CH_0 δ 175.9, 159.4, 138.0, 130.6, 128.0, 44.1; IR (neat) 2954, 2857, 1727, 1514, 1469, 1385,

1250, 1104, 1041, 836, 777 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{56}NaO_7Si$ (M+Na): 663.3693, found: 663.3703.



(*E*)-(4*S*,6*R*,7*R*)-7-((benzyloxy)methoxy)-1-hydroxy-6- ((4-methoxybenzyl)oxy) octan-4-yl-5- ((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl pent-3-enoate (1.99). To a stirring solution of olefin **1.98** (12.4 g, 18.9 mmol, 1.0 equiv) in THF (25 mL) under an argon atmosphere in a 250 ml rb flask, was added 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 114 mL, 56.8 mmol, 3.0 equiv). Stirring continued for 10 min at rt, and then the solution was placed into a H_2O bath and sonicated at 60 Hz for 45 min. The solution was removed from the sonication bath and cooled to 0° C. A 2M aqueous NaOH solution (45 mL) and a 30% aqueous H_2O_2 solution (18 mL) were added. Stirring continued for 1 h at 0° C. The reaction mixture was quenched by transfer into a 1 L separatory funnel that contained a mixture of EtOAc (300 mL) and H_2O (200 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 10.0 cm silica gel column, eluting with 30% EtOAc/ hexanes, collecting 125 mL fractions. The product containing fractions (9-45) were combined and concentrated under reduced pressure to yield alcohol **1.99** (9.20 g, 74%) as a clear oil: R_f = 0.21 (30 % EtOAc/Hex.); $[\alpha]_D^{20}$ = +28.0 (*c* = 1.0,

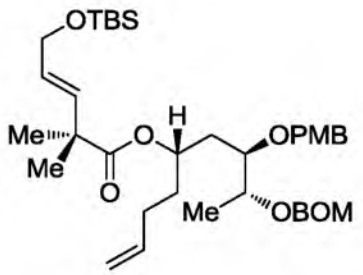
$CHCl_3$); 500 MHz ^1H NMR ($CDCl_3$) δ 7.38-7.22 (m, 7H), 6.88-6.83 (m, 2H), 5.86 (ddd, *J* = 17.6, 2.0, 2.0 Hz, 1H), 5.61 (ddd, *J* = 20.5, 4.9, 4.9 Hz, 1H), 5.17 (dddd, *J* = 9.0, 6.1, 4.9, 4.9 Hz, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 2H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.36 (d, *J* = 10.3 Hz, 1H), 4.17 (dd, *J* = 4.9, 1.5 Hz, 2H), 3.95 (dq, *J* = 6.4, 4.9 Hz, 1H), 3.79 (s, 3H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.42 (ddd, *J* = 10.3, 4.9, 2.0 Hz, 1H), 1.85-1.79 (m, 1H), 1.79-1.68 (m, 1H), 1.60-1.51 (m, 4H), 1.30 (s, 3H), 1.30 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 176.2, 159.4, 138.0, 134.8, 130.6, 130.0, 128.6, 128.1, 127.9, 127.9, 114.0, 93.5, 77.6, 73.3, 73.1, 71.2, 69.6, 64.0, 62.6, 55.5, 44.2, 35.0, 31.4, 28.4, 26.1, 25.3, 25.1, 18.6, 15.3, -5.0 ; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 26.2, 25.3, 25.1, 15.4, -4.9; CH_2 δ 93.5, 73.1, 69.6, 64.0, 62.6, 35.0, 31.4, 28.4; CH_1 δ 134.8, 130.0, 128.7, 128.1, 128.0, 127.9, 114.1, 77.6, 73.3, 71.3; CH_0 δ 176.2, 159.4, 138.0, 130.6, 44.2, 18.6; IR (neat) 3478, 2951, 2858, 1723, 1613, 1513, 1464, 1385, 1148, 1039, 836, 777, 698 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{58}NaO_8NaSi$ (M+Na): 681.3799, found: 681.3802.



(*E*)-(4*S*,6*R*,7*R*)-7-((benzyloxy)methoxy)-6-((4-methoxybenzyl)oxy)-1-oxooctan-4-yl-5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl pent-3-enoate. To a stirring solution of alcohol **1.99** (19.2 g, 29.1 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) in a 500 ml rb flask at -5° C, was added $(iPr)_2NEt$ (35 mL, 204.0 mmol, 7.0 equiv) and DMSO

(20 mL, 291.4 mmol, 10.0 equiv). Stirring continued for 10 min at -5° C, and then SO_3•Py (18.6 g, 116.6 mmol, 4.0 equiv) was added in three portions over 15 min. The reaction was allowed to proceed for 1 h at -5 °C, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (150 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 15.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (29-86) were combined and concentrated under reduced pressure to yield aldehyde (17.9 g, 93%) as a clear yellow oil: R_f = 0.54 (50 % EtOAc/Hex.); $[\alpha]_D^{20}$ = +24.0 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.23 (t, J = 1.5 Hz, 1H), 7.39-7.24 (m, 7H), 6.88-6.84 (m, 2H), 5.86 (ddd, J = 15.6, 1.5, 1.5 Hz, 1H), 5.62 (ddd, J = 15.6, 4.9, 4.9 Hz, 1H), 5.17 (m, 1H), 4.82 (d, J = 6.8 Hz, 1H), 4.78 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.52 (d, J = 10.3 Hz, 1H), 4.34 (d, J = 10.3 Hz, 1H), 4.17 (dd, J = 4.9, 1.5 Hz, 2H), 3.96 (dq, J = 6.4, 4.9 Hz, 1H), 3.79 (s, 3H), 3.42 (ddd, J = 10.7, 4.9, 2.4 Hz, 1H), 2.44 (t, J = 7.8 Hz, 2H), 1.96 (dddd, J = 12.2, 7.8, 7.8, 4.4 Hz, 1H), 1.89-1.77 (m, 2H), 1.63-1.59 (m, 1H), 1.58-1.55 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.18 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 201.4, 176.1, 159.5, 138.0, 134.4, 130.5, 130.0, 128.6, 128.4, 127.9, 127.9, 114.0, 93.5, 77.5, 73.1, 73.0, 70.7, 69.6, 63.8, 55.5, 44.2, 39.9, 34.9, 27.5, 26.2, 25.4, 25.1, 18.6, 15.2, -4.9 ; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 26.2, 25.4, 25.1, 15.2, -4.9; CH_2 δ 93.5, 73.1, 69.7, 63.9, 40.0, 34.9, 27.5; CH_1 δ 201.4, 134.4, 130.0, 128.7, 128.4, 127.9, 127.9, 114.0, 77.5, 73.0, 70.7; CH_0 δ

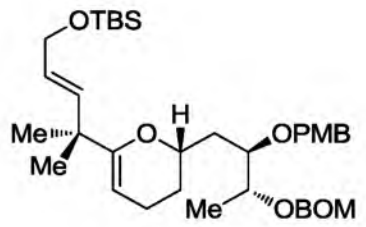
176.1, 159.5, 138.0, 130.5, 44.2, 18.6; IR (neat) 2931, 2857, 1725, 1514, 1464, 1386, 1249, 1111, 1040, 836, 778 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{56}O_8NaSi$ (M+Na): 679.3642, found: 679.3654.



(*E*)-(5*S*,7*R*,8*R*)-8-((benzyloxy)methoxy)-7-((4-methoxy benzyl)oxy) non-1-en-5-yl 5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl pent-3-enoate (1.87). To a stirring suspension of methyltriphenylphosphonium bromide (9.0 g, 25.4 mmol, 2.0 equiv) in THF (85 mL) in a 250 ml rb flask at -5 °C under argon, was added *n*-BuLi (1.8 M in hexanes, 9.3 mL, 16.5 mmol, 1.3 equiv). The solution was stirred at rt for 30 min, which resulted in a yellow-orange colored solution of the Wittig reagent.

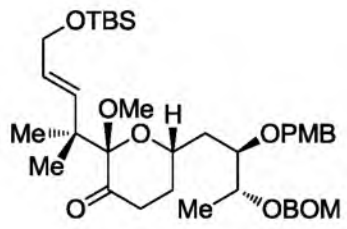
To a stirring solution of aldehyde (8.3 g, 12.7 mmol, 1.0 equiv) and THF (30 mL) in a 50 mL at -5 °C, was added Wittig reagent dropwise via cannula over 30 min. The reaction was allowed to proceed for 5 min at -5 °C, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by transfer into a 1 L separatory funnel that contained a mixture of a saturated aqueous pH 7 buffer solution (200 mL) and 20% EtOAc/hexanes (350 mL). The phases were separated and the aqueous phase was extracted with 20% EtOAc/hexanes (2 × 200 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 16.0 cm

silica gel column, eluting with 5% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (33-49) were combined and concentrated under reduced pressure to yield olefin **1.87** (6.2 g, 74%) as a clear oil: R_f = 0.52 (20 % EtOAc/Hex.); $[\alpha]_D^{20}$ = +24.5 (*c* = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.25 (m, 7H), 6.88-6.83 (m, 2H), 5.88 (ddd, *J* = 15.6, 1.5, 1.5 Hz, 1H), 5.76 (dddd, *J* = 16.6, 10.3, 6.4, 6.4 Hz, 1H), 5.62 (ddd, *J* = 15.6, 4.9, 4.9 Hz, 1H), 5.18 (dddd, *J* = 9.8, 6.6, 5.3, 2.9 Hz, 1H), 5.00 (dddd, *J* = 16.5, 1.6, 1.6, 1.6 Hz, 1H), 4.95 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.81 (d, *J* = 7.1 Hz, 1H), 4.78 (d, *J* = 7.1 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 10.3 Hz, 1H), 4.37 (d, *J* = 10.3 Hz, 1H), 4.17 (dd, *J* = 4.9, 1.5 Hz, 2H), 3.94 (dq, *J* = 6.4, 6.3 Hz, 1H), 3.80 (s, 3H), 3.41 (ddd, *J* = 10.3, 4.9, 2.0 Hz, 1H), 2.09-2.01 (m, 2H), 1.80 (ddd, *J* = 14.2, 9.8, 2.0 Hz, 1H), 1.72-1.60 (m, 3H), 1.31 (s, 3H), 1.31 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 176.1, 159.4, 138.1, 138.1, 134.7, 130.7, 130.0, 128.6, 128.1, 128.0, 127.9, 115.0, 114.0, 93.5, 77.7, 73.4, 73.2, 71.2, 69.6, 64.0, 55.5, 44.2, 35.1, 34.5, 29.6, 26.2, 25.4, 25.2, 18.6, 15.3, -4.9; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 26.2, 25.4, 25.2, 15.4, -4.9; CH_2 δ 115.0, 93.5, 73.2, 69.6, 63.9, 35.1, 34.5, 29.5; CH_1 δ 138.1, 134.7, 130.0, 128.6, 128.1, 128.0, 127.9, 114.0, 77.7, 73.4, 71.2; CH_0 δ 176.1, 159.4, 138.1, 130.7, 44.2, 18.6; IR (neat) 2931, 2857, 1725, 1514, 1413, 1464, 1249, 1147, 1105, 1042, 836, 777 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{58}O_7NaSi$ (M+Na): 677.3850, found: 677.3850.



(((*E*)-4-((*S*)-2-((2*R*,3*R*)-3-((benzyloxy)meth oxy) -2-((4-methoxybenzyl) oxy)butyl)-3,4-dihydro-2*H*-pyran-6-yl)-4-methylpent-2-en-1-yl) oxy)(*tert*-butyl)dimethylsilane (1.86). To a stirring solution of titanium(IV) chloride (15.6 mL, 141.8 mmol, 15.0 equiv) in CH_2Cl_2 (600 mL) in a 2 L rb flask at 0 °C under argon, was added THF (80 mL) to give a golden yellow solution. The solution was stirred at 0 °C for 10 min, then TMEDA (135.0 mL, 907.3 mmol, 96.0 equiv) was added dropwise, resulting in a color change to brown. The solution was stirred at rt for 30 min, then activated zinc (22.2 g, 340.2 mmol, 36.0 equiv) and lead(II) chloride (5.3 g, 18.9 mmol, 2.0 equiv) were added in one large portion. A series of color changes occured, ultimately resulting in a blue-green solution. A solution of olefin **1.87** (6.2 g, 9.5 mmol, 1.0 equiv) and 1,1-dibromoethane (13.8 mL, 151.2 mmol, 16.0 equiv) in CH_2Cl_2 (150 mL) was added slowly over 20 min via an addition funnel. The addition funnel was rinsed with additional CH_2Cl_2 (10 mL) and slowly added to the reaction mixture. The addition funnel was removed and the mixture was heated at reflux for 2 h, then cooled to 0 °C and quenched by the addition of saturated aqueous potassium carbonate solution (110 mL). The resulting solution was stirred at 0 °C for 30 min, and was then filtered through a 3 cm alumina pad. The reaction flask was washed with CH_2Cl_2 (300 mL) and filtered. This procedure was repeated 2 more times. The filtrate was concentrated under reduced pressure, and the resulting solid was filtered and washed with 50% EtOAc/hexanes (500 mL) in order to remove salts prior to chromatography Purification was accomplished by flash column chromatography using a

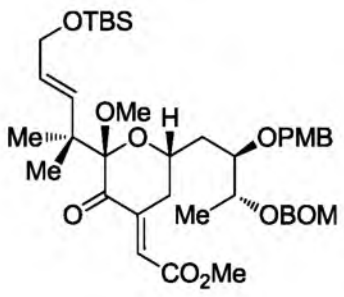
10.0 × 10.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (3-18) were combined and concentrated under reduced pressure to yield cyclic enol ether **1.86** (4.7 g, 80%) as a clear yellow oil: R_f = 0.39 (5 % EtOAc/toluene); $[\alpha]_D^{20}$ = +37.9 (*c* = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.23 (m, 7H), 6.88-6.84 (m, 2H), 5.75 (ddd, *J* = 15.6, 1.5, 1.5 Hz, 1H), 5.52 (ddd, *J* = 15.6, 10.3, 5.4, 5.4 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.82 (d, *J* = 7.3 Hz, 1H), 4.69-4.60 (m, 3H), 4.55 (dd, *J* = 4.4, 2.9 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.14 (dd, *J* = 5.4, 1.5 Hz, 2H), 4.01 (dddd, *J* = 9.8, 9.8, 2.0, 2.0 Hz, 1H), 3.95 (dq, *J* = 6.4, 6.4 Hz, 1H), 3.83 (ddd, *J* = 10.7, 5.4, 2.5 Hz, 1H), 3.80 (s, 3H), 2.08 (dddd, *J* = 17.1, 9.8, 6.8, 2.9 Hz, 1H), 2.02-1.84 (m, 1H), 1.80 (ddd, *J* = 14.2, 10.3, 2.0 Hz, 1H), 1.75 (ddd, *J* = 13.7, 6.8, 3.4 Hz, 1H), 1.61 (ddd, *J* = 13.2, 10.7, 2.4 Hz, 1H), 1.36-1.25 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.17 (s, 3H), 1.17 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 159.3, 159.1, 138.7, 138.1, 131.1, 129.6, 128.6, 128.0, 127.8, 125.9, 114.0, 93.6, 93.2, 78.0, 74.1, 73.6, 71.6, 69.6, 64.6, 55.4, 40.5, 36.4, 28.4, 26.2, 26.1, 26.0, 20.6, 18.6, 15.8, -4.8; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 26.2, 26.1, 25.9, 15.8, -4.8; CH_2 δ 93.6, 73.6, 69.5, 64.6, 36.4, 28.3, 20.6; CH_1 δ 138.7, 129.6, 128.6, 128.0, 127.8, 125.9, 114.0, 93.2, 78.0, 74.1, 71.7; CH_0 δ 159.3, 159.1, 138.1, 131.1, 40.5, 18.6; IR (neat) 2930, 2856, 1661, 1581, 1462, 1381, 1249, 1098, 1042, 837, 776 cm ^{1}; HRMS (ESI) calcd for $C_{37}H_{56}NaO_6Si$ (M+Na): 647.3744, found: 647.3750.



(2*S*,6*S*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((*E*)-5-((*tert*-butyldimethyl silyl)oxy)-2-methylpent-3-en-2-yl)-2- methoxydihydro-2*H*- pyran-3(4*H*)-one (1.85). To a stirring solution of magnesium monoperoxyphthalic acid (80%, 12.7 g, 20.5 mmol, 2.0 equiv) and $NaHCO_3$ (8.6 g, 102.4 mmol, 10.0 equiv) in CH_2Cl_2/MeOH (1:1, 70 mL) in a 250 ml rb flask at 0° C, was added glycal **1.86** (6.4 g, 10.2 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) dropwise via cannula. The flask was rinsed with an additional CH_2Cl_2 (5 mL) and slowly added to the reaction mixture. TLC analysis after 3 h at 0° C indicated complete consumption of the enol ether starting material. The reaction mixture was quenched by transfer into a 1 L separatory funnel that contained a mixture of a saturated aqueous H_2O (350 mL) and EtOAc (200 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 200 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude intermediate alcohol as a clear light yellow oil. This material was carried onto the next step without further purification.

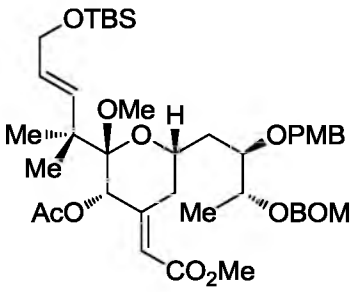
To a stirring solution of previously described crude alcohol in CH_2Cl_2 (100 mL) in a 250 ml rb flask at rt, was added oven dried 4 Å molecular sieves (13.0 g) and *N*-methylmorpholine-*N*-Oxide (3.6 g, 30.7 mmol, 3.0 equiv). Stirring continued for 10 min and then tetrapropylammonium perruthenate (358 mg, 1.0 mmol, 0.1 equiv) was added. Stirring continued for 1 h, then the reaction was filtered through a 4 cm pad of silica gel. The silica pad was washed with EtOAc (3 × 100 mL). The resulting solution was

concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 10.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 125 mL Erlenmeyer flask fractions. The product containing fractions (25-41) were combined and concentrated under reduced pressure to yield ketone **1.85** (4.6 g, 66% over 2 steps) as a clear yellow oil: R_f = 0.44 (30 % EtOAc/hexanes); $[\alpha]_D^{20}$ = +15.2 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.19 (m, 7H), 6.87-6.82 (m, 2H), 5.50 (ddd, *J* = 16.1, 1.5, 1.5 Hz, 1H), 5.50 (ddd, *J* = 16.1, 5.4, 5.4 Hz, 1H), 4.85 (dd, *J* = 10.3, 6.8 Hz, 1H), 4.66 (s, 2H), 4.63 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 10.7 Hz, 1H), 4.14 (dd, *J* = 4.9, 1.5 Hz, 2H), 4.13-4.07 (m, 2H), 3.88 (dq, *J* = 3.4, 2.0 Hz, 1H), 3.79 (s, 3H), 3.23 (s, 3H), 2.43 (dd, *J* = 8.3, 5.4 Hz, 2H), 2.00-1.83 (m, 3H), 1.80 (ddd, *J* = 14.2, 10.3, 2.0 Hz, 1H), 1.68 (ddd, *J* = 14.3, 10.3, 2.4 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 207.5, 159.3, 138.0, 136.1, 130.7, 129.4, 128.6, 127.9, 127.8, 127.7, 113.9, 104.2, 93.5, 77.3, 72.6, 72.1, 70.1, 69.6, 64.2, 55.4, 52.3, 44.1, 37.7, 36.4, 30.2, 26.1, 22.9, 22.2, 18.5, 14.9, -5.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 52.3, 26.2, 22.9, 22.2, 14.9, -5.0; CH_2 δ 93.5, 72.2, 69.6, 64.2, 37.7, 36.4, 30.2; CH_1 δ 136.1, 129.4, 128.6, 128.0, 127.9, 127.8, 114.0, 77.3, 72.6, 70.1; CH_0 δ 207.5, 159.3, 138.0, 104.2, 44.1, 18.5; IR (neat) 2950, 2857, 1723, 1612, 1513, 1463, 1382, 1249, 1112, 837, 737, 698 cm ^{1}; HRMS (ESI) calcd for $C_{38}H_{58}NaO_8Si$ (M+Na) 693.3799, found 693.3802.



(*E*)-methyl 2-((2*S*,6*S*)-6-((2*R*,3*R*)-3-((benzyl oxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((*E*)-5-((*tert*-butyldimethylsilyl)oxy) -2-methylpent-3-en-2-yl)-2-methoxy-3-oxodihydro-2*H*-pyran-4(3*H*)-ylidene) acetate (1.103). To a stirring solution of the ketone **1.85** (3.72 g, 5.54 mmol, 1.0 equiv) in MeOH (55 mL) in a 100 ml rb flask at rt, was added K_2CO_3 (2.30 g, 16.6 mmol, 3.0 equiv) followed by methyl glyoxylate (1.24 M in THF, 11.2 mL, 13.9 mmol, 2.5 equiv). The reaction was allowed to proceed for 1 h at rt, after which time TLC analysis indicated complete consumption of the ketone starting material. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The mixture was diluted with H_2O (150 mL) and Et_2O (200 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 200 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 5.0 × 10.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (9-28) were combined and concentrated under reduced pressure to yield enoate **1.103** (3.36 g, 82%) as a bright yellow oil: R_f = 0.53 (4:5:1 CH_2Cl_2/hexanes/Et_2O); $[\alpha]_D^{20}$ = -28.1 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.15 (m, 7H), 6.84-6.79 (m, 2H), 6.53 (q, *J* = 2.0 Hz, 1H), 5.81 (ddd, *J* = 15.6, 1.5, 1.5 Hz, 1H), 5.40 (ddd, *J* = 16.1, 5.4, 5.4 Hz, 1H), 4.85 (dd, *J* = 10.7, 6.8 Hz, 2H), 4.66 (s,

2H), 4.61 (d, J = 10.7 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.18-4.08 (m, 2H), 4.06 (ddd, J = 5.4, 3.9, 2.0 Hz, 2H), 3.89 (dq, J = 3.4, 2.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.31 (ddd, J = 18.6, 2.0, 2.0 Hz, 1H), 3.20 (s, 3H), 2.85 (ddd, J = 19.1, 12.7, 3.4 Hz, 1H), 1.96 (ddd, J = 14.2, 8.8, 2.0 Hz, 1H), 1.75 (ddd, J = 14.2, 10.3, 2.9 Hz, 1H), 1.21 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.8, 166.2, 159.4, 148.2, 138.1, 134.8, 130.6, 129.3, 128.8, 128.7, 128.0, 127.9, 122.7, 114.0, 104.8, 93.6, 76.9, 72.4, 71.8, 69.7, 69.5, 64.1, 55.4, 52.2, 52.0, 44.7, 36.2, 36.1, 26.1, 22.5, 22.0, 18.5, 14.7, -5.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 52.2, 51.9, 26.1, 22.5, 22.0, 14.7, -5.0; CH_2 δ 93.6, 71.8, 69.7, 64.1, 36.2, 36.1; CH_1 δ 134.8, 129.3, 128.8, 128.7, 128.1, 127.9, 122.7, 114.0, 76.9, 72.4, 69.5; CH_0 δ 197.8, 166.2, 159.4, 148.2, 138.1, 130.6, 104.8, 44.7, 18.5; IR (neat) 2952, 2886, 2856, 1724, 1706, 1514, 1250, 1109, 1043, 835, 777 cm ^{1}; HRMS (ESI) calcd for $C_{41}H_{60}NaO_{10}Si$ (M+Na) 763.3853, found 763.3856.



(*E*)-methyl 2-((2*S*,3*S*,6*S*)-3-acetoxy-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((*E*)-5-((*tert*-butyldimethy lsilyl)oxy) -2-methylpent -3-en-2-yl)-2-methoxydihydro -2*H*-pyran-4(3*H*)-ylidene)acetate (1.84). To a stirring solution of the ketone **1.103** (2.23 g, 3.0 mmol, 1.0 equiv) in MeOH (74 mL) in a 500 ml rb flask at rt, was added $CeCl_3 \cdot 7H_2O$ (22.2 g, 60.2 mmol, 20.0 equiv). The mixture was stirred until all the $CeCl_3 \cdot 7H_2O$ was completely dissolved. The mixture was then cooled

to -40 °C and then $NaBH_4$ (766 mg, 20.2 mmol, 10.0 equiv) was added in one portion. Stirring continued for 1 h at -40 °C, after which the reaction was quenched by slow addition of saturated aqueous NH_4Cl solution (100 mL) and diluted with 50% EtOAc/hexanes (200 mL). The phases were separated, and the aqueous phase was extracted with 50% EtOAc/hexanes (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and carefully concentrated under reduced pressure to provide the crude alcohol was used in the next step without purification.

To a stirring solution of crude alcohol and DMAP (367 mg, 3.00 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL, 0.02 M) in a 250 mL rb flask at 0 °C, was added a mixture of acetic anhydride (1.4 mL, 15.0 mmol, 5.0 equiv) and pyridine (4.9 mL, 60.2 mol, 20.0 equiv) dropwise via syringe. The solution was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and stirred for 1 h. The phases were separated and the aqueous phase was extracted with 50% EtOAc/hexanes (2 × 100 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 5.0 × 16.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (7-21) were combined and concentrated under reduced pressure to yield ester **1.84** (2.1 g, 87%) as a clear oil: R_f = 0.41 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -1.1 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.14 (m, 7H), 6.84-6.81 (m, 2H), 6.00 (ddd, *J* = 15.6, 1.5, 1.5 Hz, 1H), 5.90-5.82 (m, 1H), 5.40 (ddd, *J* = 16.1, 5.3, 5.3 Hz, 1H), 5.37 (s, 2H), 4.87 (d, *J* = 7.3 Hz, 1H), 4.84 (d, *J* = 7.4 Hz, 1H), 4.66 (d, *J* = 1.9 Hz, 2H), 4.61 (d, *J* = 10.7 Hz, 1H), 4.41 (d, *J* = 10.7 Hz, 1H), 4.17-4.09 (m, 2H), 4.03 (dddd, *J* = 12.4, 9.2, 2.7, 2.7 Hz, 1H), 3.89 (dq, *J* = 4.3, 1.9 Hz, 1H),

3.78 (s, 3H), 3.68 (s, 3H), 3.51 (dd, J = 15.6, 8.5 Hz, 1H), 3.23 (s, 3H), 2.29 (ddd, J = 14.6, 12.1, 1.9 Hz, 1H), 2.03 (s, 3H), 1.92 (ddd, J = 14.2, 10.2, 2.0 Hz, 1H), 1.73 (ddd, J = 14.6, 10.2, 2.4 Hz, 1H), 1.22 (d, J = 6.4 Hz, 3H), 1.10 (s, 6H), 0.89 (s, 9H), 0.05 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 169.0, 166.2, 159.0, 152.2, 138.0, 137.8, 130.3, 129.2, 128.3, 127.6, 127.5, 124.0, 117.3, 113.6, 102.5, 93.1, 76.6, 72.1, 71.8, 71.7, 69.3, 68.3, 64.3, 55.0, 51.4, 50.9, 45.6, 36.2, 32.3, 25.1, 24.6, 23.1, 21.1, 18.3, 14.5, -5.1; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.0, 51.4, 51.0, 25.9, 24.6, 23.1, 21.1, 14.5, -5.1; CH_2 δ 93.1, 71.7, 69.3, 64.3, 36.1, 32.3; CH δ 138.1, 129.2, 128.3, 127.6, 127.5 124.1, 117.3, 113.7, 76.6, 72.1, 71.8, 68.3; CH_0 δ 169.0, 106.2, 159.0, 152.2, 137.8, 130.3, 102.5, 45.6, 18.3. IR (neat) 2952, 2886, 2856, 1747, 1720, 1613, 1514, 1462, 1373, 1249, 1158, 1107, 1043, 836, 777, 689 cm^{-1}; HRMS (ESI) calcd for $C_{43}H_{64}NaO_{11}Si$ (M+Na) 807.4116, found 807.4129.

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CHAPTER 2

THE SYNTHESIS AND THE BIOLOGICAL PROFILE OF FLUORESCENT BRYOSTATIN ANALOGS

Introduction

The secondary messenger 1,2-diacylglycerol (DAG) is an important regulator of a wide range of cellular functions such as apoptosis, differentiation, cell growth, and tumor-promotion. The response to DAG is mediated by a superclass of receptors including protein kinase C (PKC), which is widely studied for its role in cell proliferation, differentiation, and apoptosis.[1] There are 2 classes of DAG-sensitive isozymes of PKC, classic PKC isozymes (α, βI, βII, γ) and calcium independent novel PKC isozymes (ε, δ, η). When DAG binds to PKC it activates the kinase and induces translocation to a subcellular compartment or membrane. This activated receptor may interact with different targeted proteins or phosphorylate substrates based on the localization of the PKC. While DAG is the endogenous activator of PKC, exogenous ligands such as phorbol esters and bryostatins can also activate the kinase. These particular ligands have a much higher binding affinity for PKC than do the DAGs.

Characterizing the translocation of PKC using PKCs labelled with green fluorescent proteins (GFPs) has proven to be a valuable tool in learning more about this event.[2] The Blumberg lab has observed that the location of PKC and the rate of translocation differ when exposed to phorbol esters of varying lipophilicity. The more lipophilic phorbol esters induce initial translocation of GFP-PKCδ to the plasma membrane

while the more hydrophilic esters resulted in initial translocationto the nuclear membrane.[3] The effect of varying ligands on the translocation of PKC is not yet well understood. A better understanding of factors driving PKCs translocation may explain why different C1 domain binding ligands show selectivity in their activation of downstream cellular pathways while having similar *in vitro* binding affinities.[4] The location and persistence of activated PKC may play a key role in determining its access to different substrates effecting activation of downstream cellular pathways. This knowledge is important to understand the DAG signaling pathway and facilitate the design of selective C1 domain binding drugs.

The Role of Phorbol Esters in the Translocation of PKC

In 2005, the Blumberg group and collaborators designed and constructed a series of brightly fluorescent phorbol ester derivatives with the purpose of observing the real time analysis of the pharmacokinetics and intracellular migration of these ligands. The synthesis of these derivatives is shown in Figure **2.1**. Details of the reagents and yields were not disclosed in the published paper. A linker between the phorbol ester **2.1** and fluorescent tag was incorporated through an esterification reaction to give **2.3**. The Fmoc carbamate was then removed using TBAF to produce the primary amine. Peptide coupling then introduced the BODIPY FL tags that varied in carbon chain length. Using acidic conditions, the triphenylmethyl ether was removed to produce fluorescent phorbol esters that varied in length (C2, C4, C10, and C15) **2.4**.

The binding affinities of the fluorescent phorbol esters are shown in Table **2.1**. The K_i values for all of the phorbol esters were measured for PKCα and PKCδ, and found to range from 1.4-210 nM. The fluorescent phorbol esters were all less potent than [20-3*H*]

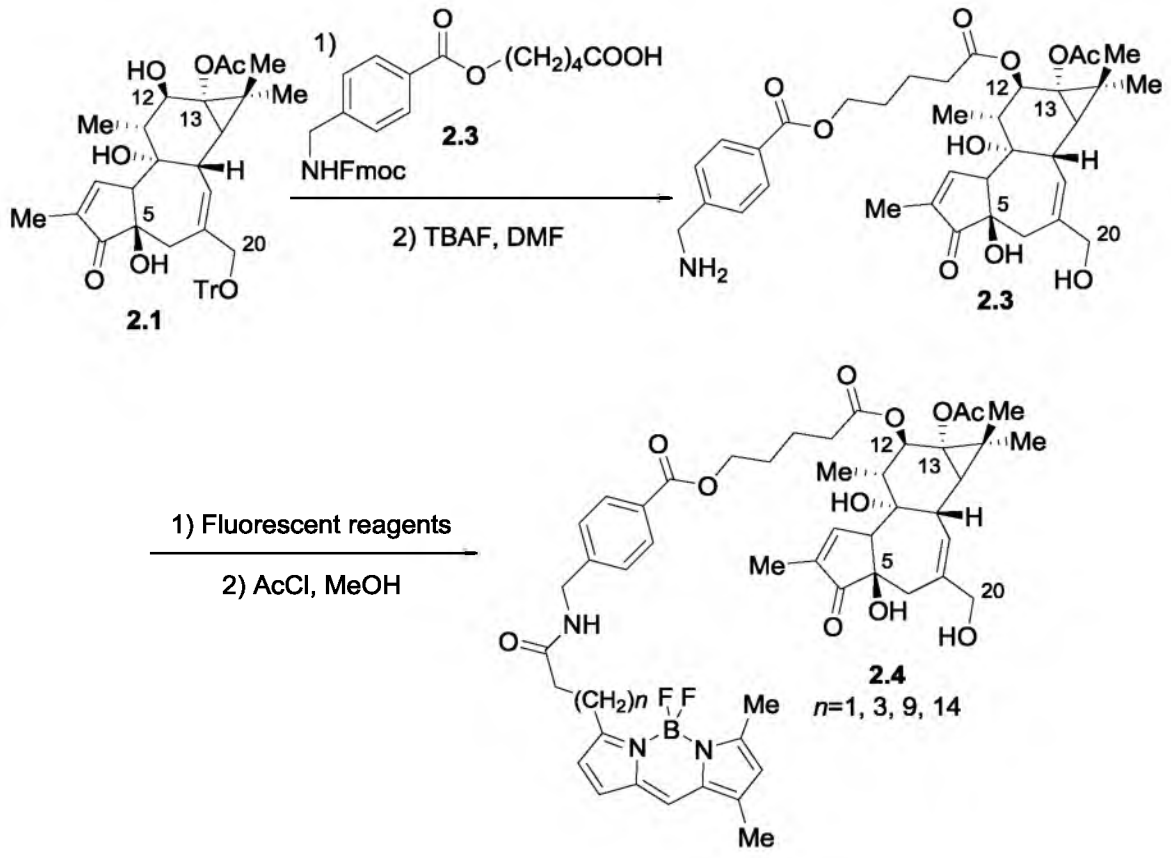


Figure 2.1. Synthesis of Fluorescent Phorbol Esters

phorbol 12,13-dibutyrate (PDBu) and showed a decrease in binding affinity as the chain length on the ester increased from C2 to C15. The decrease in binding affinity was attributed to poor solubility of the fluorescent derivatives in aqueous media, so this measurement was assayed with an increased incubation time of 30 min. The K_i values then became similar across different phorbol esters in PKCδ. For example, PE-BDFL-C15 (phorbol ester-BODIPY FL tag- C15) has a binding affinity for PKCδ of 199 nM at 5 min, but after 30 min had an affinity of 31 nM.

Using both fluorescent phorbol esters and fluorescent PKC, the Blumberg group

Table 2.1. Binding Properties of Fluorecent Phorbol Esters

Ligand	Receptor binding (K*i* nmol/L)		
	PKCα, 5-min	PKCδ, 5-min	PKCδ, 30-min
PDBu	0.30 ± 0.05	0.39 ± 0.004	
PE-BDFL-C2	1.4 ± 0.1	3.0 ± 0.2	1.5 ± 0.1
PE-BDFL-C4	6.0 ± 0.3	4.8 ± 0.4	2.8 ± 0.2
PE-BDFL-C10	16.0 ± 0.5	8.1 ± 0.4	2.2 ± 0.0
PE-BDFL-C15	211 ± 17	199 ± 26	31.2 ± 0.4

was able to simultaneously compare the distribution of ligand and receptor. This was accomplished using CHO (Chinese hamster ovary) cells that were transfected with plasmids expressing fusions of PKCα and PKCβ to DsRed (red fluorescent protein). These cells were then treated with the BODIPY FL tagged phorbol esters and visualized in real time using laser scanning confocal microscopy. The results from the C2 and C10 phorbol esters with PKCα-DsRed are shown in Figure **2.2**. A patchy translocation pattern of PKCα-DsRed to the plasma membrane was found regardless of the lipophilicity of the phorbol ester. The C2 phorbol ester (PE-BDFL-C2) showed very little colocalization with PKCα-DsRed and was located in the perinuclear area. In contrast, the duration of C10 phorbol ester (PE-BDFL-C2) colocalization with PKCα-DsRed in the plasma membrane increased significantly. The predominant location of the lipophilic phorbol esters ligands eventually shifted to the perinuclear membrane area, but at a lower rate.

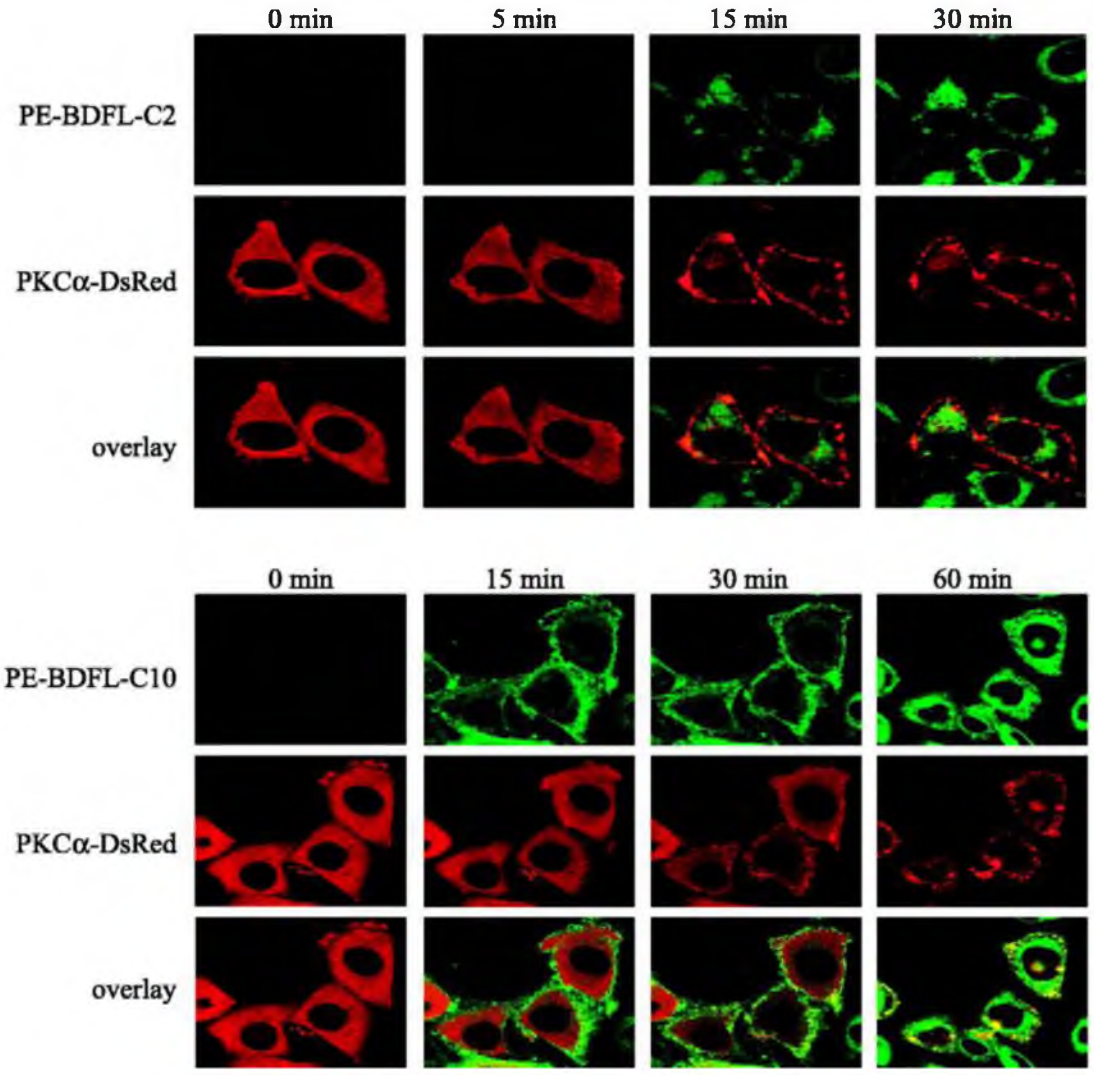


Figure 2.2. Visualization of Fluorescent Phorbol Esters with PKCα

PKCδ-DsRed translocates similarly toPKCα-DsRed (Figure **2.3**). Phorbol esters like PE-BDFL-C2 showed perinuclear colocalization with PKCδ, whereas the more hydrophobic phorbol esters like PE-BDFL-C15 showed initial cytoplasmic membrane localization. Over time the PE- BDFL-C15 moved primarily to the nuclear membrane. The differences observed in translocation are thought to be due to the lipophilicity of the phorbol ester, which affects the rate of uptake and persistence within the lipid membrane.

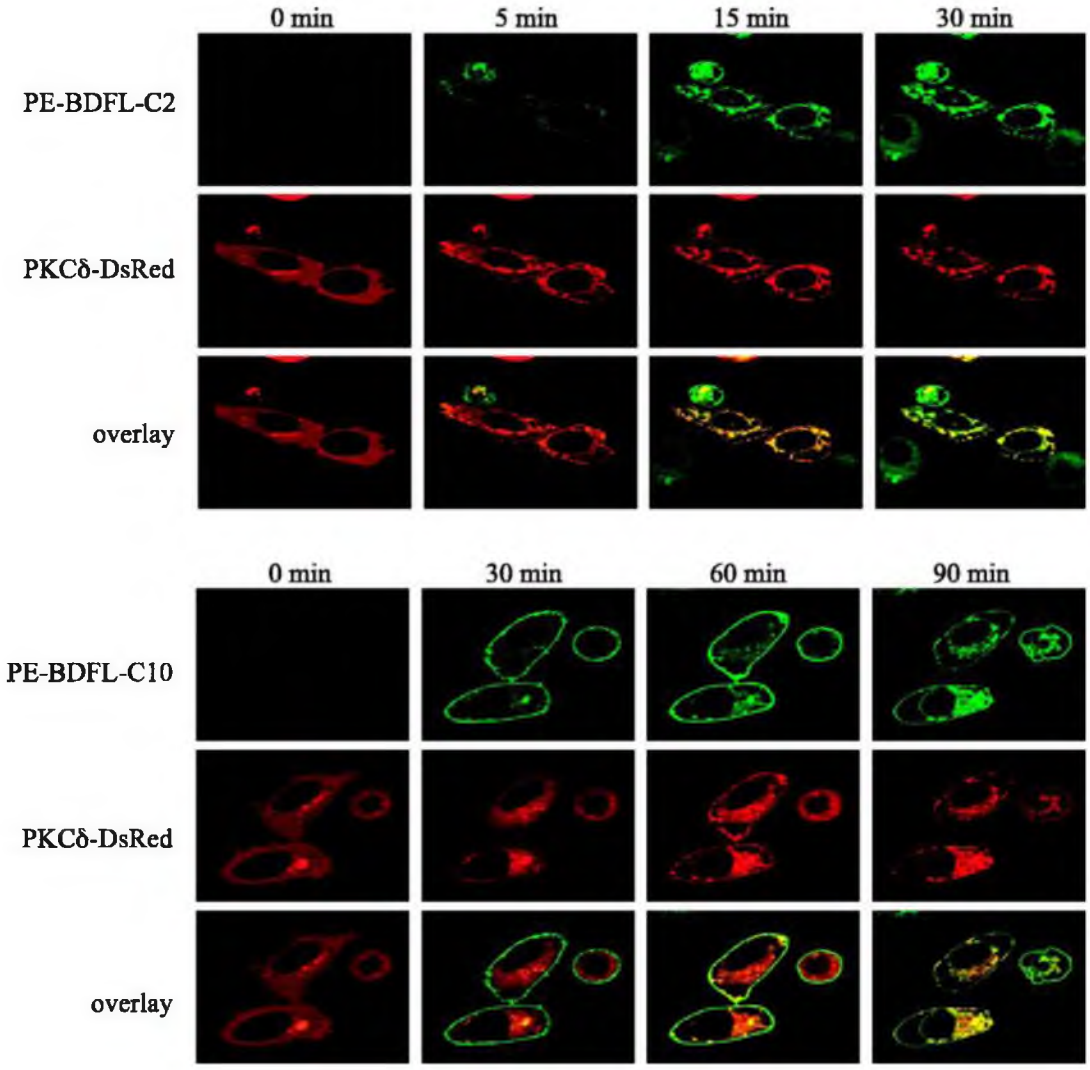


Figure 2.3. Visualization of Fluorescent Phorbol Esters with PKCδ

The Proposed Pharmacophoric Elements of the Bryostatins

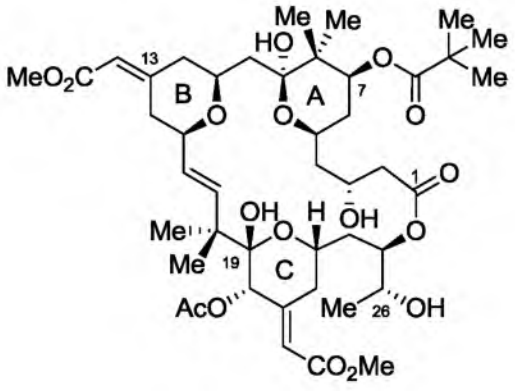
In 1988, a collaborative effort between the Wender, Blumberg and Petit groups led to the first series of structure activity relationship (SAR) studies of the bryostatins.[5] These studies compared semisynthetic bryostatins and bryostatin natural products. Comparing the binding affinities across bryostatin 1-10, 16, 17, and 18, showed that changing the esters group at the C7 and C20 positions did not increase or decrease the binding affinity significantly. When bryostatin 5 and bryostatin 16 were compared, a significant loss in

binding affinity was observed (Figure **2.4**). Bryostatin 16 lacks the C19-C20 oxidations, and as a result loses its internal hydrogen bonding network. Additional correlations between binding affinity and structure were gained from semi-synthetic bryostatins. Two analogs, **2.5** and **2.6**, were obtained from the hydrogenation of bryostatin 1. Both analogs had a reduced C20 α,β,γ,δ-ester and C13 enoate. Analog **2.6** had an additional reduction of the C21 enoate bond causing a substantial decrease in binding affinity. Acetylation of the C26 alcohol of bryostatin 4 had the most dramatic effect, essentially eliminating the analogs binding affinity for PKC.

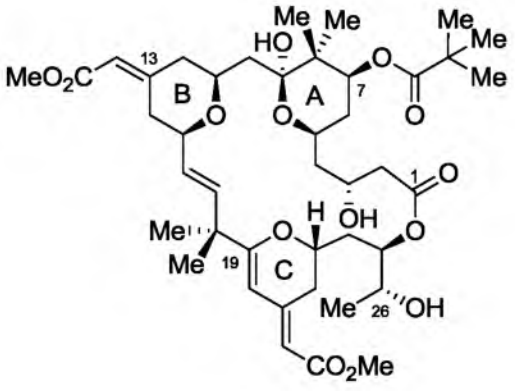
The Wender group also compared the structure of DAG, phorbol esters, and bryostatin using SAR and computational methods. From these comparisons a pharmacophore was proposed (Figure **2.5**). It was proposed that all 3 PKC ligands shared a common binding motif, a heteroatom triad that interacts with the C1 domain of PKC through hydrogen bonds. It was suggested that the C1, C19, and C26 oxygens of bryostatin are the main pharmacophores responsible for binding to PKC. These atoms corresponded to the C4, C9, and C20 oxygen atoms in phorbol, respectively. From these studies 2 hypotheses were developed. The first was that the southern portion of bryostatin is the region important for binding to PKC. The second was that the northern half of bryostatin serves as a 'spacer domain' that holds the pharmacophoric region in a rigid conformation providing proper orientation for binding.

Simplified Bryostatin Analogs

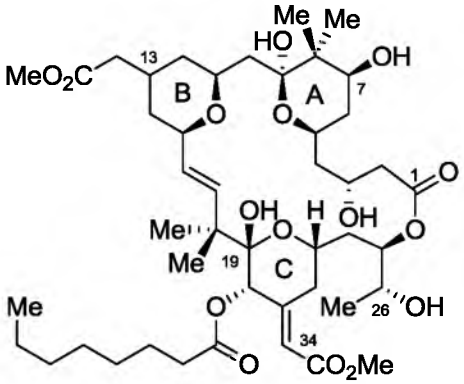
In 2008, the Keck group prepared structurally simplified analogs of bryostatin that rivaled or exceed the activity of bryostatin 1 itself.[6] The most biologically studied



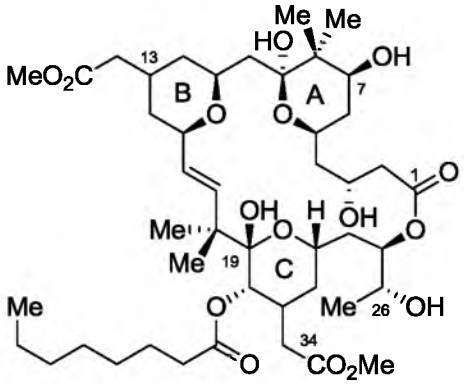
bryostatin 5
K_i= 1.04 ± 0.1 nM



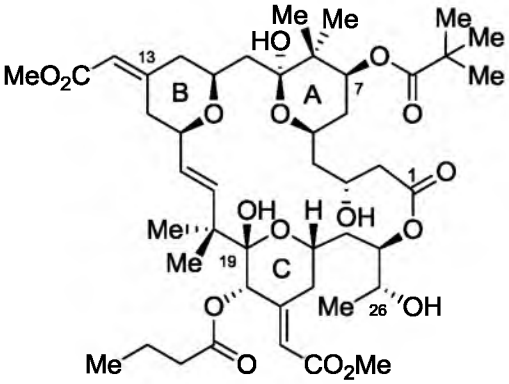
bryostatin 16
K_i= 118 ± 2 nM



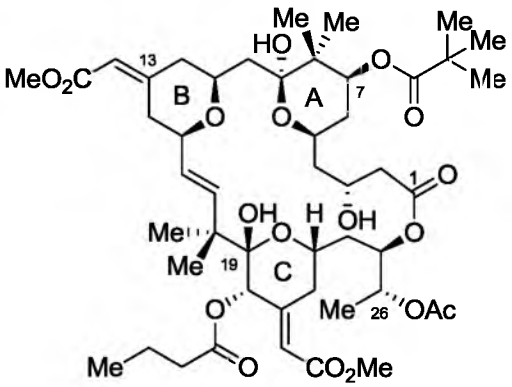
2.5
K_i= 9.61 ± 0.94 nM



2.6
K_i= 473 ± 96 nM



bryostatin 4
K_i= 1.30 ± 0.19 nM



2.7
K_i>> 100 nM

Figure 2.4. Structure Activity Relationships of Bryostatin Compounds

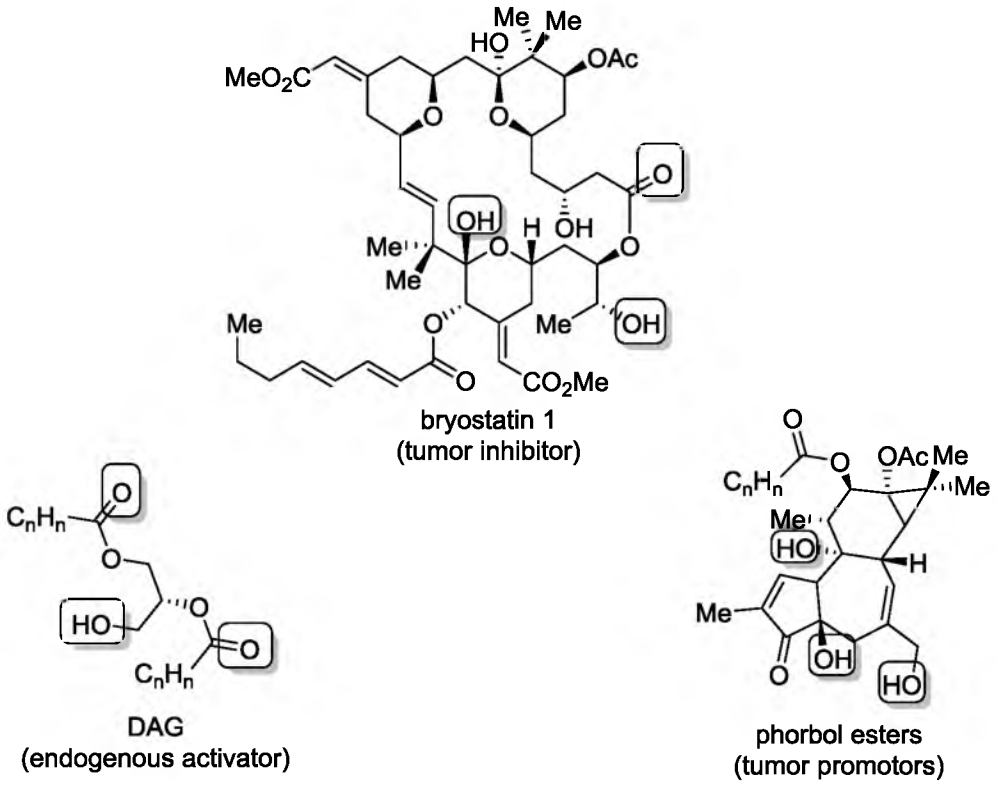


Figure 2.5. PKC Ligand Binding Hypothesis

bryostatin analog constructed by the Keck group was Merle 23 (Figure **2.6**, part **A**).[7] Merle 23 differs from bryostatin 1 at 4 positions across the northern half. This analog omits the C9 alcohol, while replacing the C7 ester and the C13 enoate exocyclic methylenes, and removing the C8 *gem*-dimethyl. These simplifications do not affect the proposed pharmacophoric elements in the southern half of the molecule that are important for binding to PKC.[8]

The Synthesis of Merle 23

The synthetic approach to Merle 23 is shown on Figure **2.6**, part **B**. The C21 exocyclic enoate would be incorporated from a ketone **2.8** via an aldol condensation and

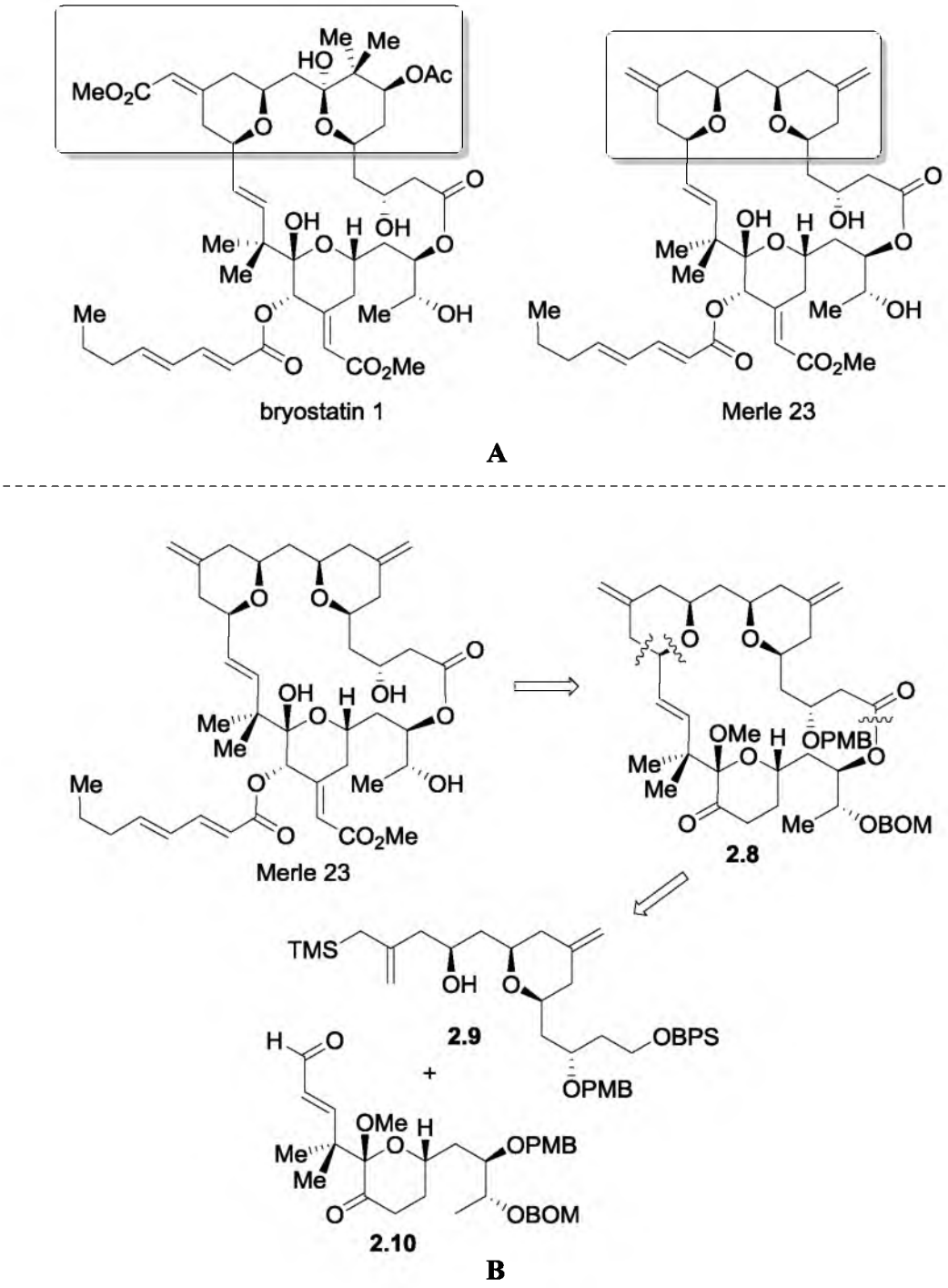


Figure 2.6. Structural Differences (A) and
Retrosynthesis of Merle 23 (B)

the C20 ester would be established by a reduction and esterification of this ketone. The A-ring **2.9** and C-ring **2.10** would be combined using the previously developed pyran annulation[9] and a Yamaguchi macrolactonization to give **2.8**.

The pyran annulation between hydroxy allyl silane **2.9** and C-ring aldehyde **2.10** provided the tricyclic macrolactone in an 82% isolated yield (Figure **2.7**). The elaboration of the C1 BPS ether to carboxylic acid **2.12** was accomplished by a selective deprotection of the BPS group using TBAF buffered with AcOH[10], followed by sequential Parikh-Doering and Pinnick oxidations. The 20 membered macrolactone was completed by removing the C25 TBS group, followed by a Yamaguchi macrolactonization to afford the desired tricyclic macrolactone **2.8** in 87% isolated yield over 2 steps. The installation of the C21 enoate involved a 2-step procedure starting with the aldol reaction of methyl glyoxylate with ketone **2.8**, followed by elimination with carbonyl diimidazole and Et_3N. A Luche reduction of the resulting ketone gave the alcohol which was immediately acylated with (2*E*,4*E*)-octa-2,4-dienoic anhydride to give protected versions of Merle 23 **2.13** as a 4:1 mixture of diastereomers at the C20 position**.** Global deprotection of the remaining protecting groups was accomplished in 2 steps. The C3 PMB ether was removed with DDQ, and the C26 BOM ether and C19 methyl ketal with $LiBF_4$.[11]

The Biological Evaluation of Merle 23

Merle 23 (K_i = 0.70 ±0.01 nM) proved to have a higher binding affinity for PKC than does bryostatin 1 (K_i = 1.35 nM). However, the binding affinity for Merle 23 was measured using pure PKCα, whereas the 1.35 nM binding affinity for bryostatin1 had been determined using a mixture of PKC isozymes isolated from rat brain. A recent

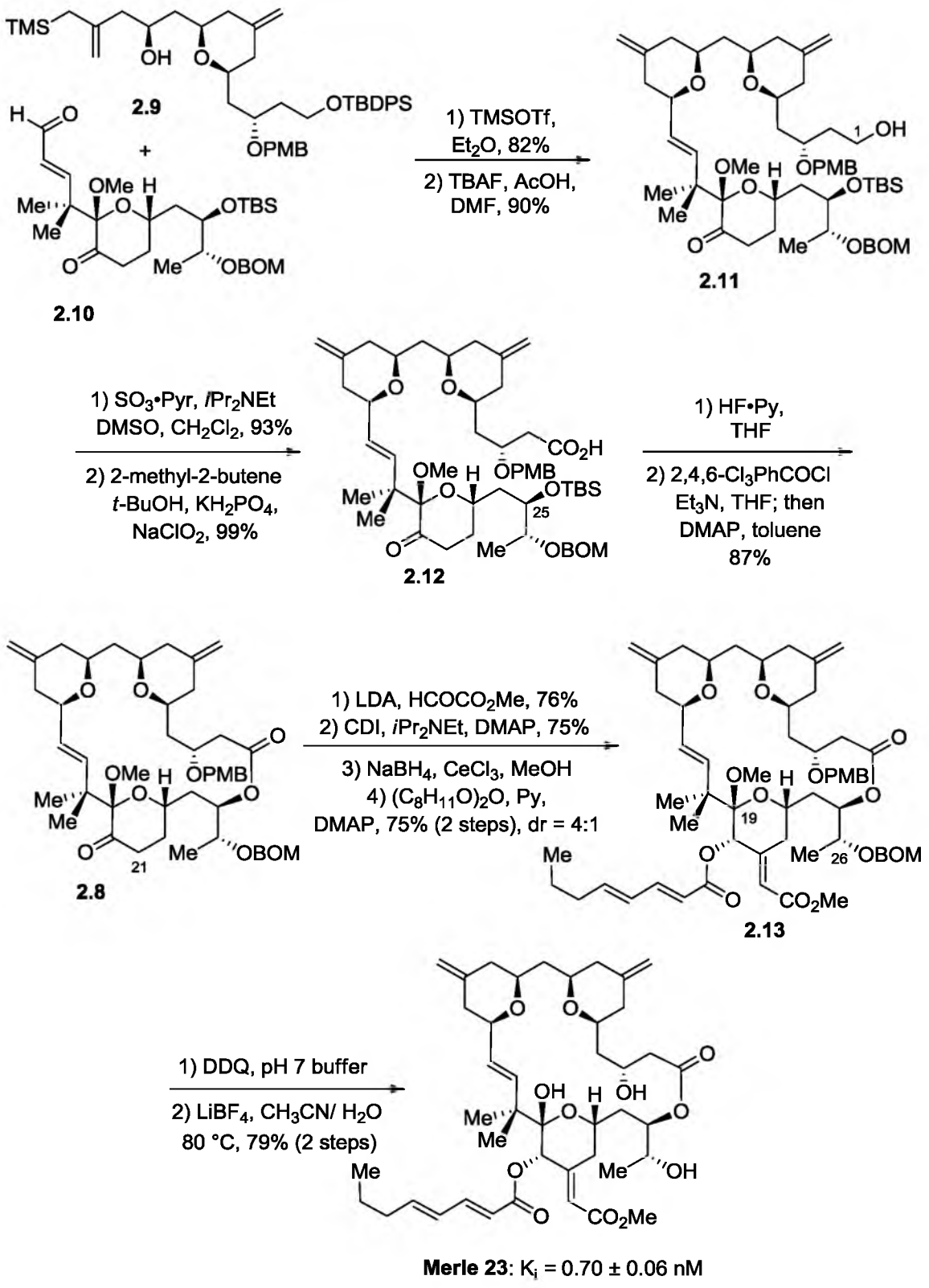
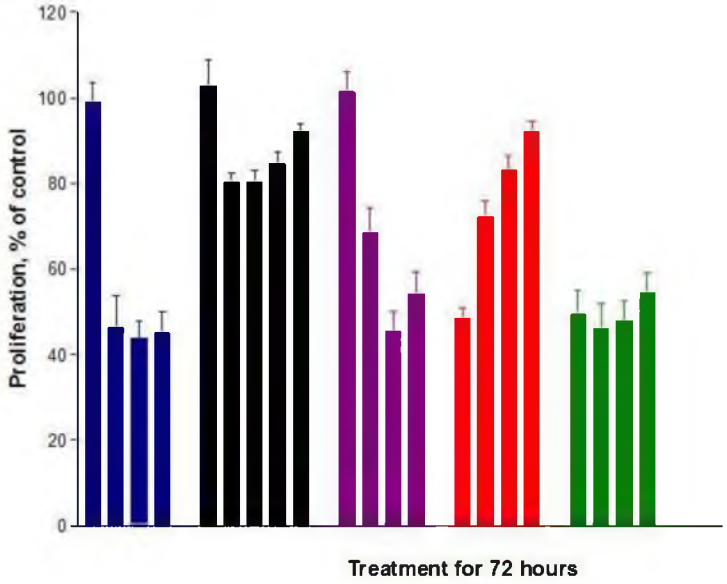


Figure 2.7. Synthesis of Merle 23

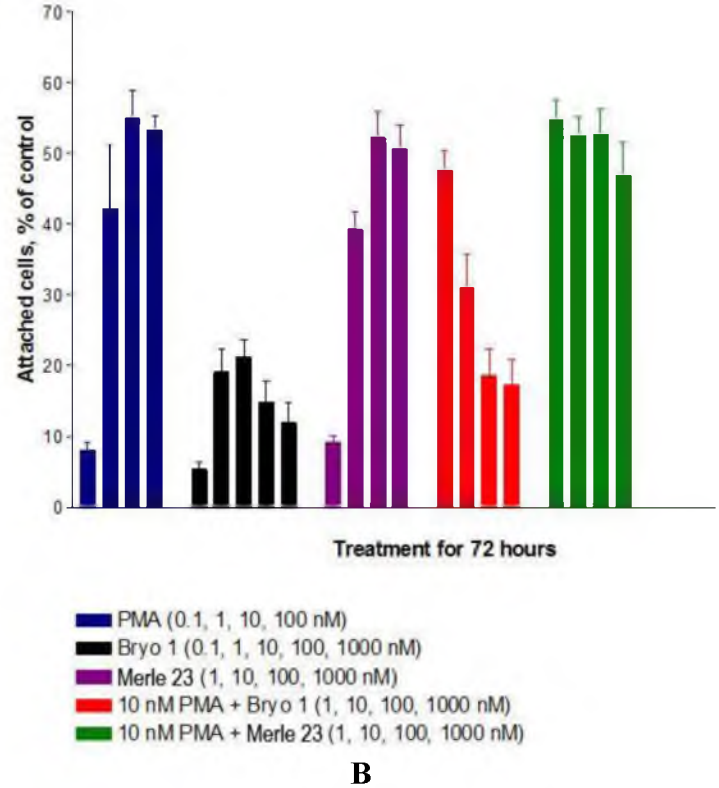
determination of K_i for bryostatin 1 gives a 0.48 ±0.03 nM for PKCα. Simply comparing binding affinities only characterizes the compounds as competent PKC ligands and does not determine if the analogs biologically mimic bryostatin. In a U937 leukemia cell assay, phorbol esters inhibit proliferation and induce attachment while bryostatin 1 fails to induce either effect.[12] Additionally, bryostatin 1 antagonizes the response induced by PMA in a dose dependent manner. This experiment was suggested and performed by Blumberg and his group at the NIH as one assay to demonstrate whether or not an analog will be 'bryostatin like.' When evaluated in this assay, Merle 23 displayed a PMA like behavior in that it both inhibits proliferation (Figure **2.8**, part **A**) and induces attachment (Figure **2.8**, part **B**). Merle 23 also does not antagonize the response to PMA like bryostatin 1 does. We concluded that the northern region must somehow be responsible for the PMA like activity of Merle 23 in the U937 cell line and is not simply a spacer domain as suggested in the literature.[8]

The Synthesis Merle 28

Due to the 'PMA-like' activity exhibited by Merle 23 in U937 cells, the functional groups on the northern half of the analog responsible for this switch were evaluated. It was hypothesized that one or more of the 4 changes (C7, C8, C9, and C13) in the molecule were responsible for this switch. In order to determine the substitution crucial for the shift, a systematic deletion of one group at a time, starting with the C30 ester, was undertaken (Figure **2.9**).[13] Synthetically, this would be the easiest analog to obtain with one of the 4 deletions because it was accessible through previously developed routes to the A-ring **2.16** and C-ring fragments **2.15**.

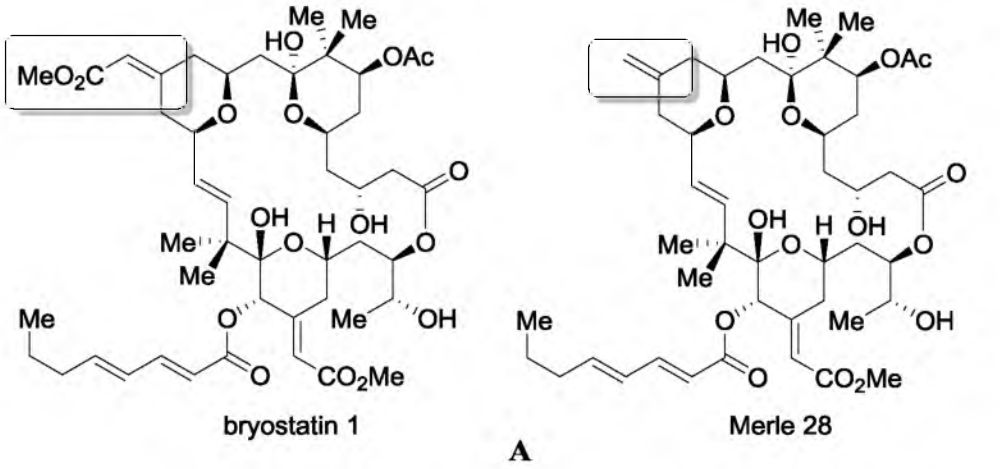


A



B

Figure 2.8. U937 Proliferation (A) and Attachment (B)



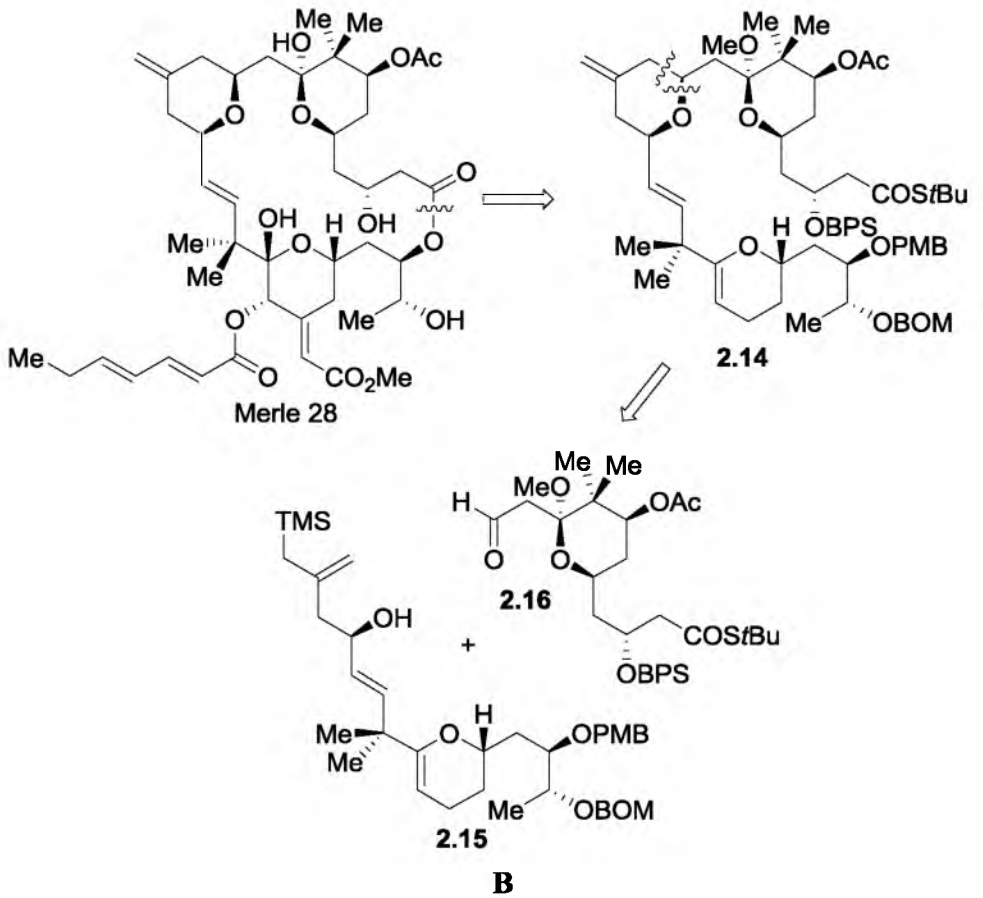


Figure 2.9. Structural Difference of Merle 28 (A) and Retrosynthesis of Merle 28 (B)

The retrosynthesis of Merle 28 is shown in Figure **2.9**. Similarly to Merle 23, the C-ring of **2.14** would be functionalized after the A-ring and C-ring were joined together. The 20-membered macrolactone would be completed through a Yamaguchi macrolactonization to construct Merle 28. The β -hydroxyallyl silane **2.15** and aldehyde **2.16** would be joined through a pyran annulation reaction.

The synthesis of the C-ring β-hydroxyallyl silane started from cyclic enol ether **2.17**.[14] This aldehyde was reacted with trimethyl(2-((tributylstannyl)methyl)allyl)silane under asymmetric allylation conditions to give C15 β-hydroxyallyl silane **2.15** (Figure **2.10**). The synthesis of A-ring **2.16** was accomplished using a previously developed procedure.[15] Both fragments were combined using TMSOTf to provide the desired tricyclic adduct **2.14** in a 58% yield. The functionalization of the C-ring began with the epoxidation of the glycal using MMPP and *in situ* opening by MeOH to provide the α-hydroxyl ketal. This alcohol was immediately oxidized using TPAP/NMO to afford C20 ketone **2.18**. Installation of the *α, β*-unsaturated methyl ester at the C21 position was accomplished using a 2-step process involving an aldol reaction of the ketone with methyl glyoxylate, followed by dehydration with CDI to deliver enoate **2.19**. The relatively low yield of 47 % was due to a side reaction at the C7 acetate position.

A Luche reduction of the C20 ketone afforded the alcohol intermediate, which was quickly esterified by reaction with (2*E*,4*E*)-octa-2,4-dienoic anhydride to provide ester **2.20** (Figure **2.11**). With all the necessary functional groups incorporated, the next step was to produce the *seco* acid for macrolactonization. This was achieved by the removal of the C3 BPS group followed by hydrolysis of the thioester. The resulting hydroxy acid was protected as the C3 TES ether, followed by removal of the C25 PMB, and

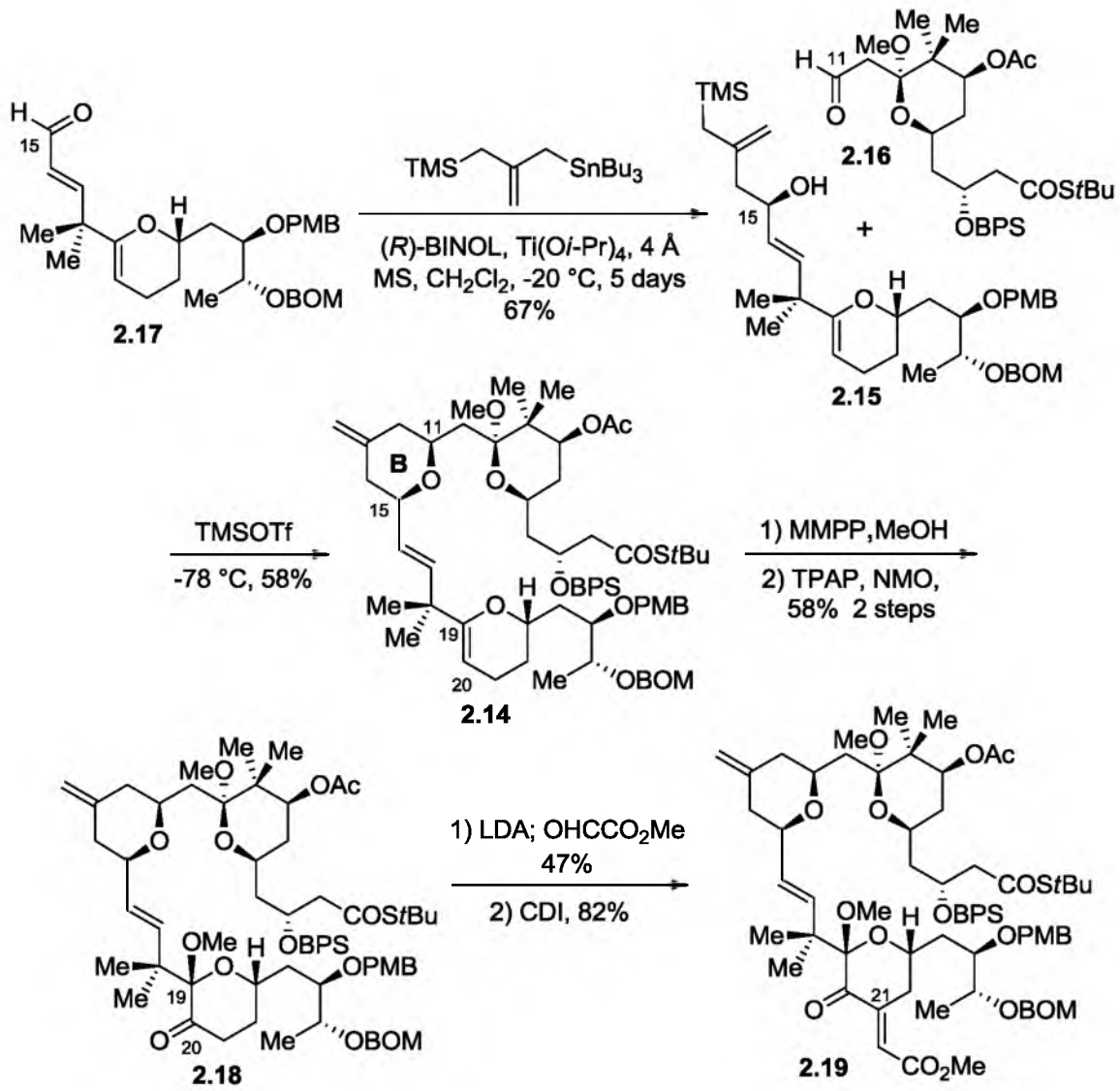


Figure 2.10. Coupling of A- and C-rings Using Pyran Annulation

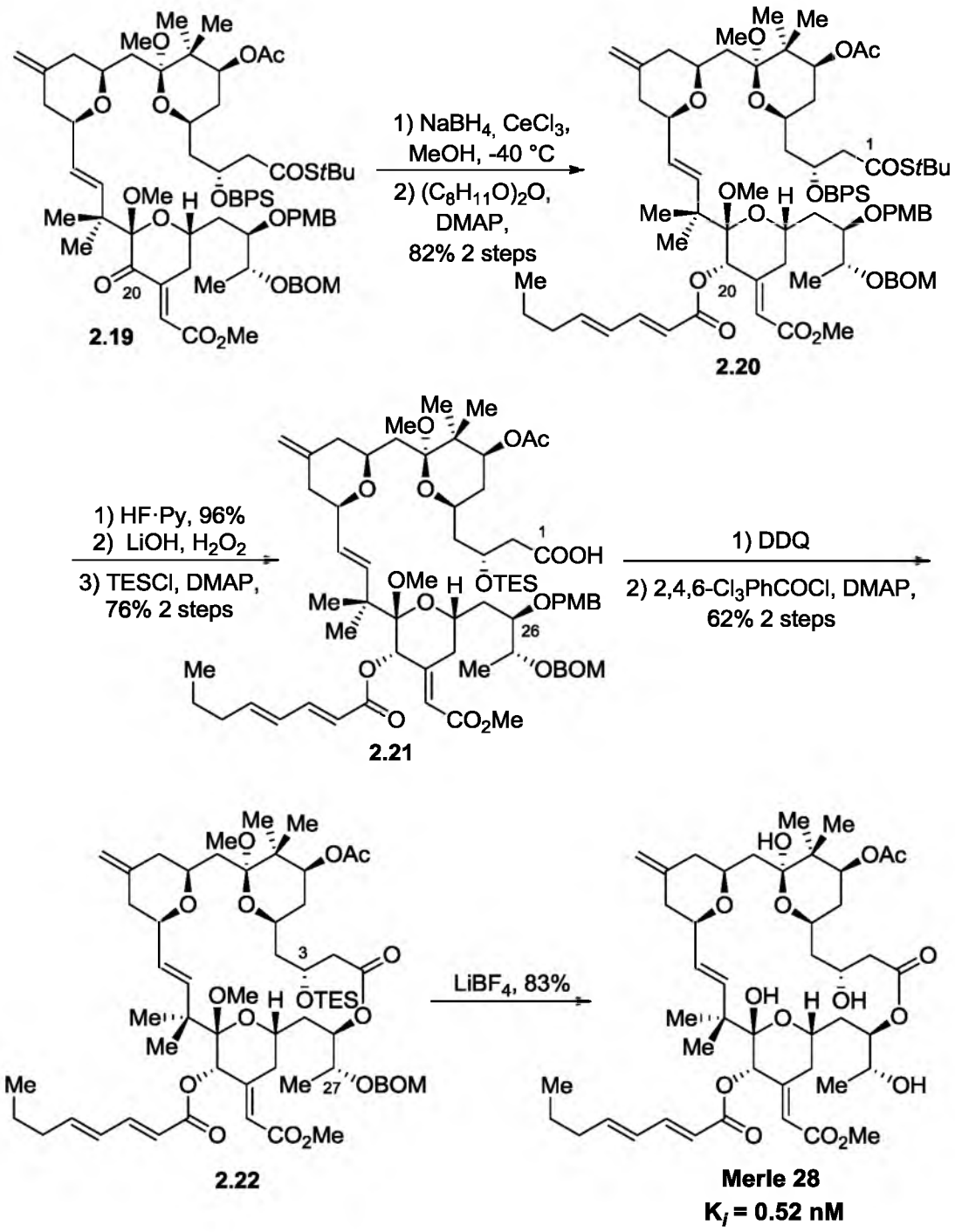


Figure 2.11. Completion of C30-decarbomethoxy Bryostatin 1

macrolactonization afforded the macrolactone **2.21**. Global deprotection using $LiBF_4$ hydrolyzed the 2 ketals, the C3 TES, and the C26 BOM ether to give the desired analog Merle 28.

The Biological Evaluation of Merle 28

Merle 28 was evaluated for PKC binding affinity and assayed for function in the U937 leukemia cell line. Merle 28 was shown to have a binding affinity of 0.52 ± 0.06 nM for PKCα. In the U937 cells, Merle 28 (numbered 12 in Figure **2.12**) resembled bryostatin 1 rather than PMA. Merle 28 resembled bryostatin 1 by giving a dose-dependent biphasic pattern in its inhibition of cell growth. When co-administered, Merle 28 proved to be a functional antagonist of PMA and blocked the effect of the phorbol ester. A similar result was obtained in the cell attachment assay where Merle 28 had a reduced level of cell attachment, similar to bryostatin 1. When co-administered, Merle 28 inhibited the attachment induced by PMA. From this U937 cell line study of Merle 28, it was found that the absence of the C30 carbomethoxy group does not decrease the binding affinity for PKCα, and does not change the bryostatin like biological activity. From these experiments it was concluded that Merle 28 is a functional analogue of bryostatin 1.

Results and Discussion

Merle 23 and Merle 28 differ from each other at only 3 positions (C7, C8, and C9), but have very different responses in U937 cells. Merle 23 acts 'PMA like' and Merle 28 acts 'bryo-like' (Figure **2.13**). We decided to investigate why these 2 structurally similar analogs have very different biological responses. Using a fluorescent version of

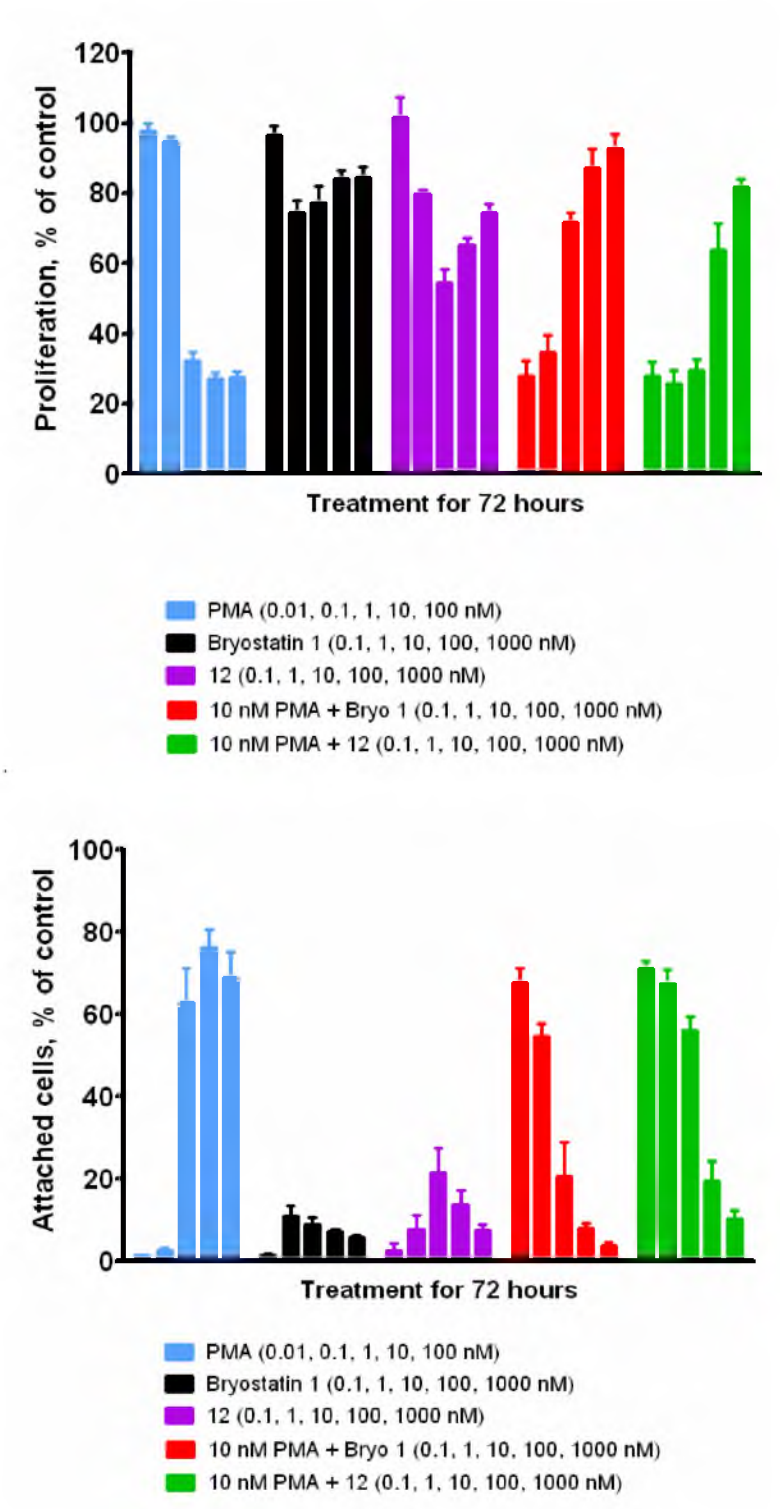


Figure 2.12. Proliferation and Attachment of U937 Cells by Merle 28

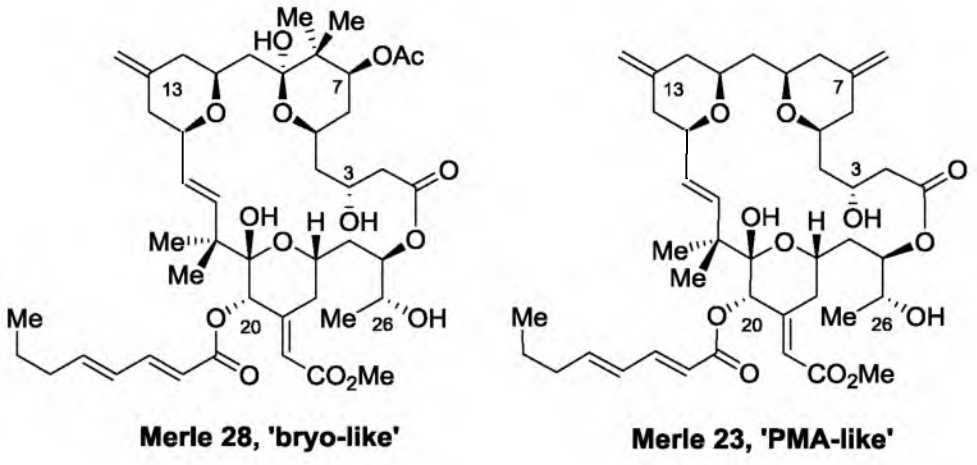


Figure 2.13. Bryostatin Analogs

these bryostatin analogs will help us understand the phenomena of PKC translocation,which is believed to be at least partially responsible for different biological responses observed with different PKC ligands. The localization of the fluorescent bryostatin analogs will be correlated to the localization of GFP-PKC isozymes. The uptake rate of the analogs by the cells may also have an effect on where PKC translocates. Since location and persistence of activated PKC plays a key role in downstream cellular pathways, these analogs might help explain what kind of cellular responses is key to 'bryo-like' activity. However, incorporating a tag may affect the binding affinity and biological responses of Merle 23 and Merle 28.

The Fluorescent Tag and the Position

The photo and chemical stability, solubility, narrow emission bands, high emission intensity, and visible excitation wavelength of BOPIPY fluorophores make it a popular tag for imaging applications. The initial studies involving BODIPY FL labeled phorbol esters used this tag to study PKC translocation.[4] Typically a BODIPY adduct is constructed

through an esterification or peptide coupling reaction.

The location of the BODIPY tag was limited to a late stage installation since its stability during many chemical manipulations was questionable. In Merle 23 and Merle 28, shown in Figure **2.13**, there are only 3 sites common for a late stage esterification reaction (C3, C20, and C26). Through semisynthetic bryostatin analogs, if the C26 alcohol is esterified the molecule loses binding affinity. It has also been observed that the C3 alcohol is very unreactive toward electrophiles due to the internal hydrogen bond network present in the bryostatin structure. Different ester groups at the C20 position on Merle 23 have been shown to have limited effects on binding and biological activity.[8, 16] For these reasons, we chose the C20 position as the best location to install the BODIPY tag.

A computational study of bryostain 1 in the C1 domain of PKC was conducted by Dr. Megan Peach from the NIH (Figure **2.14**).[17] The model shows that bryostatin 1's C20 side chain sticks outside of the binding pocket. This model adds validity to the hypothesis that the BODIPY side chain should not have a large affect on binding affinity if placed on the C20 ester position.

The Retrosynthetic Analysis of Fluorescent Merle 23 (Merle 44)

Figure **2.15** shows the retrosynthetic plan for the synthesis of Merle 44 (fluorescent Merle 23). The BODIPY ester was to be constructed through a hydrolysis of protected intermediate **2.24**. The main difference in this approach is the utilization of a fully functionalized C-ring **2.25** in the pyran annulation with A-ring **2.26**. This synthetic approach would avoid difficult manipulations on complex substrates and reduces the number of steps from the longest linear sequence. The A-ring **2.26** would be constructed

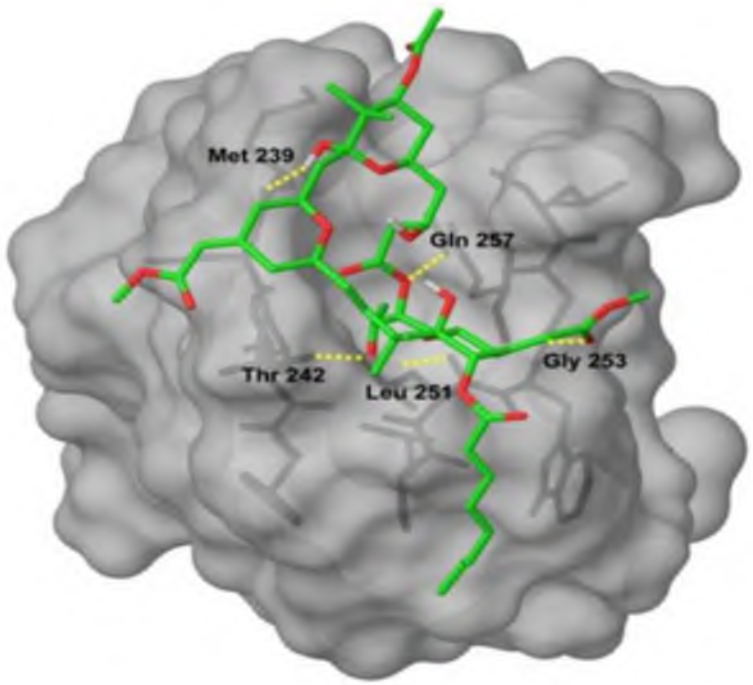


Figure 2.14: A Space Filling Model for the Docking of Bryostatin 1 to the PKC C1 Domain

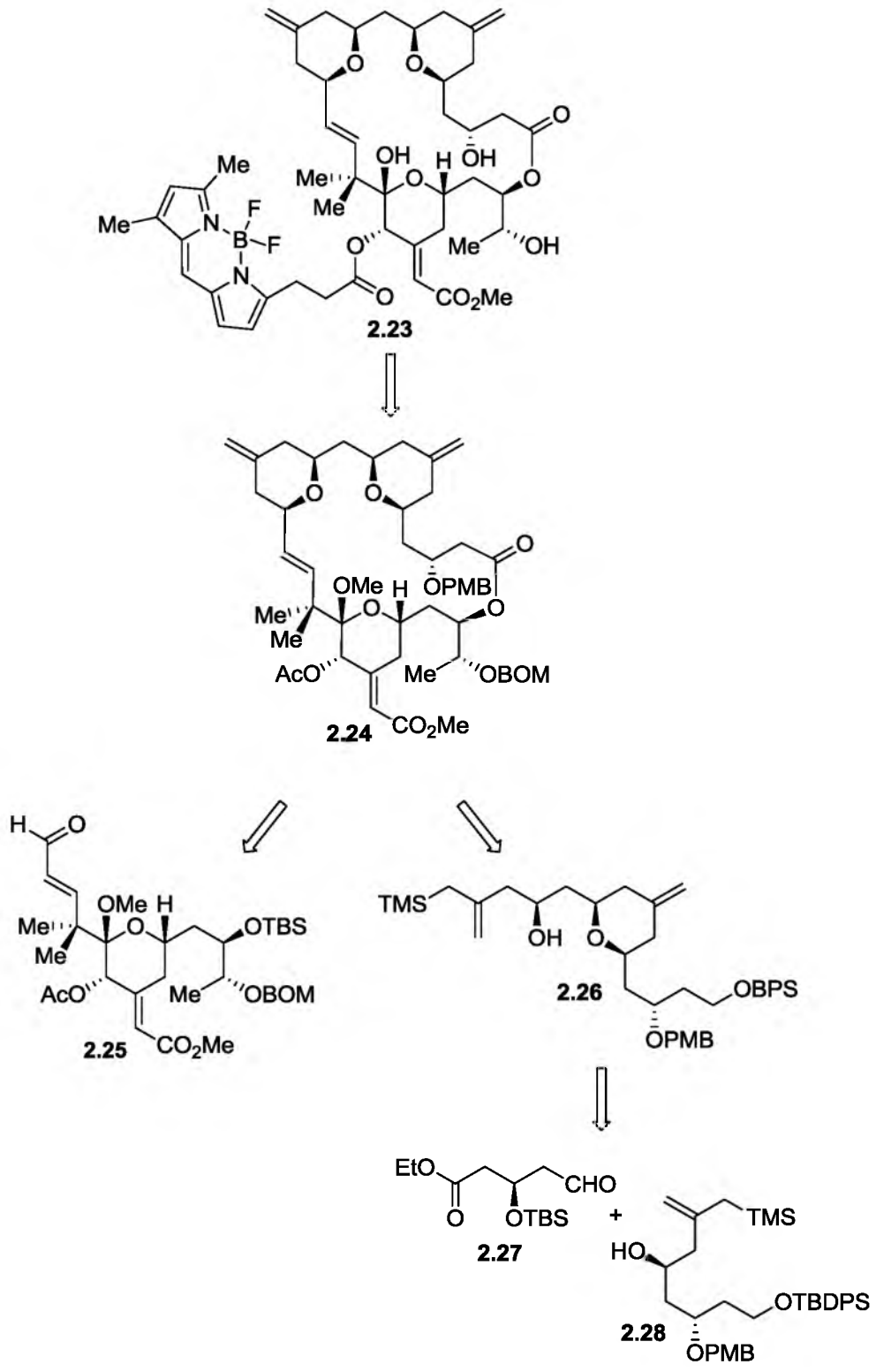


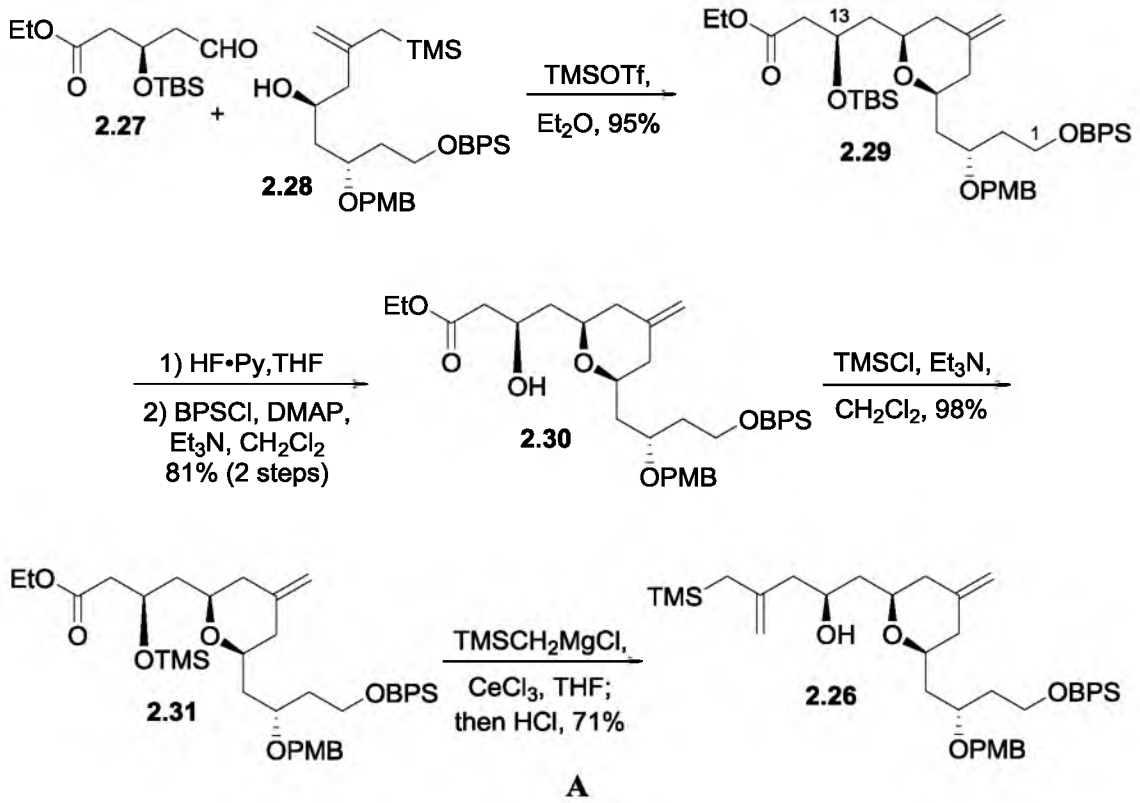
Figure 2.15. Retrosynthesis of Merle 44

using a previously developed procedure by a pyran annulation between **2.27** and **2.28**.[6]

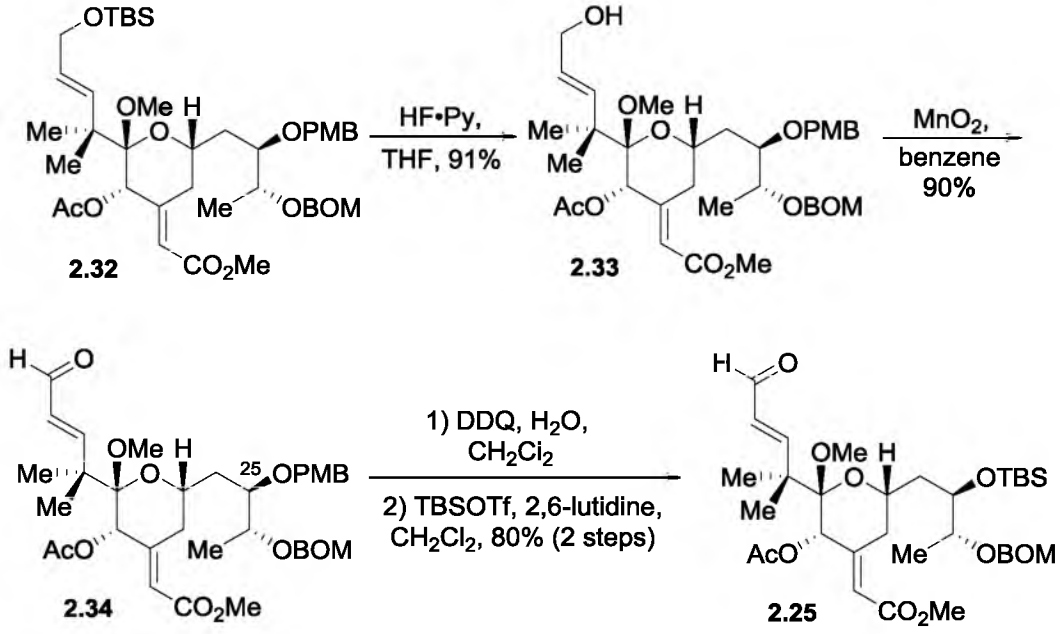
The Synthesis of Macrolactone **2.24**[16]

The A-ring intermediate **2.29** was prepared by Dr. Petersen using a pyran annulation reaction between the hydroxy allylsilane **2.27** and aldehyde **2.28** (Figure **2.16**, part **A**).[6] This material was utilized by the removal of the C13 TBS ether, which resulted in a mixture of the mono alcohol **2.30** and the C1 BPS deprotected diol. To circumvent this problem, HF•py was used to remove both the C1 and C13 silyl ethers, and then reprotected selectively using BPSCl, giving **2.30** as a single product. The C13 alcohol was then protected as the TMS ether **2.31** and a Bunnelle reaction[18] was used to install the β-hydroxyallylsilane **2.26**. The C-ring enal **2.25** was constructed by the removal of the TBS ether and oxidation of the resulting allylic alcohol to give **2.34** (Figure **2.16**, part **A**). The C25 PMB ether was then swapped for a TBS ether, giving the desired alcohol **2.25**.

A pyran annulation reaction between fully functionalized C-ring aldehyde **2.25** and β-hydroxyallylsilane **2.26** provided the tricyclic byropyran core **2.35** in 95% yield (Figure **2.17**). The macrolactonization of **2.35** follows the same steps that were reported during the synthesis of Merle 23. This sequence starts by a deprotection of the C1 BPS ether, followed by consecutive oxidations using Parikh-Doering and Pinnick reactions to give the C1 carboxylic acid **2.37**. The C25 TBS ether is then removed, followed by a Yamaguchi macrolactonization to afford the desired tricyclic macrolactone **2.24**. This route shows a significant improvement in the methodology to construct bryostatin analogs by incorporating a fully functionalized C-ring in the pyran annulation.



A



B

Figure 2.16. Synthesis of A-ring β-hydroxyallylsilane **2.26** (A) and C-ring Enal **2.25** (B)

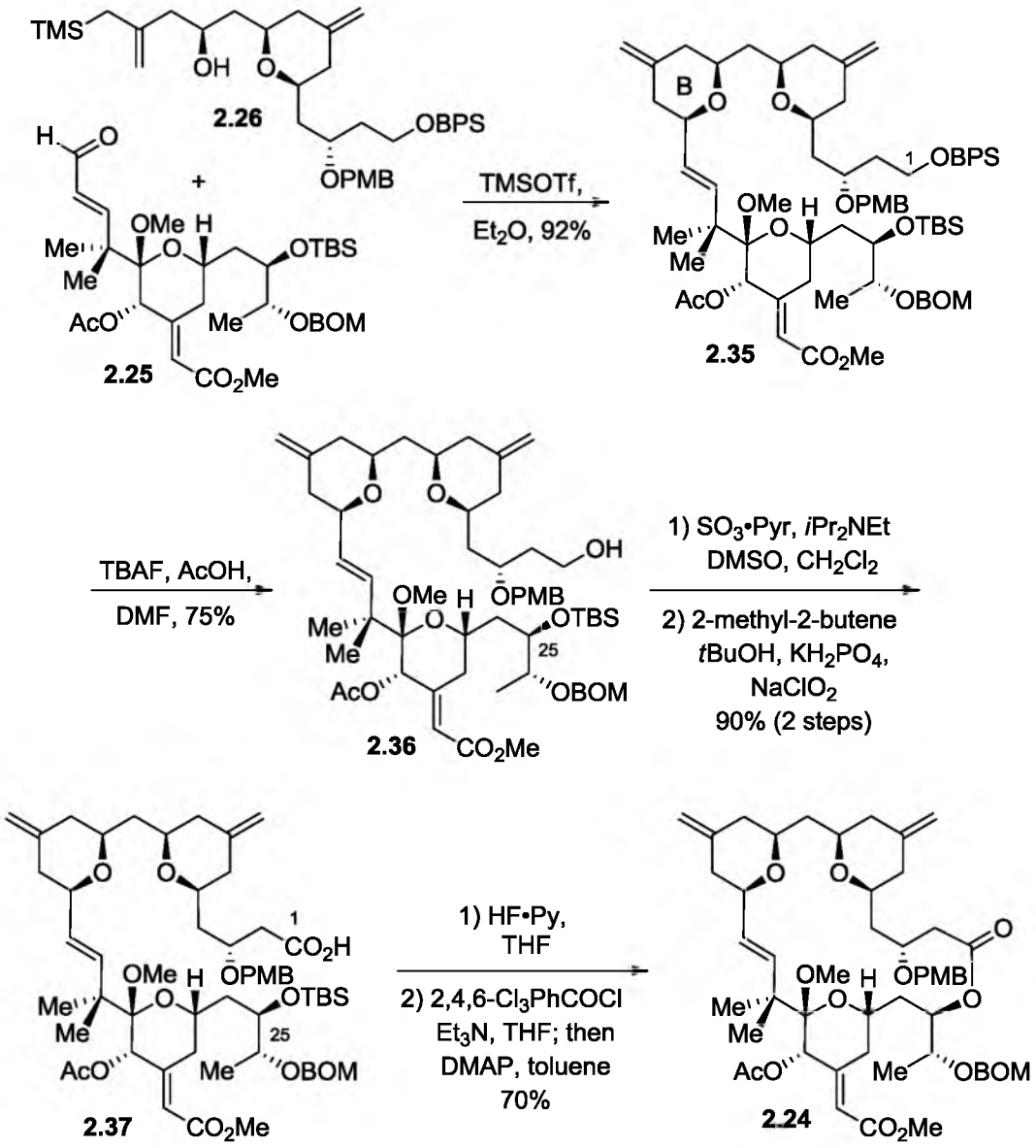


Figure 2.17. Pyran Annulation and Yamaguchi Esterification

Installation of the BOPDIY Tag

With intermediate **2.24** constructed, an investigation into installing the fluorescent tag commenced. The preparation of the BODIPY FL acid started from the commercially available pyrrole-2-carbaldehyde using a previously developed procedure (Figure **2.18**).[19] A Horner–Wadsworth–Emmons reaction between aldehyde **2.38** and ethyl (triphenylphosphoranylidene)acetate followed by hydrogenation of the olefin gave pyrrole ester **2.39** in a 78% yield over 2 steps. A Vilsmeier-Haack reaction on 2,4-dimethyl-1*H*-pyrrole gave aldehyde **2.40**. Pyrrole **2.39** and **2.40** were condensed using $POCl_3$, and then treated with $BF_3 \bullet OEt_2$ to produce BODIPY FL ester **2.41** in one pot. The ethyl ester was removed using aqueous hydrochloric acid to provide acid **2.42**.

A model study was devised to install the BODIPY FL tag and to test the stability of the resulting ester (Figure **2.19**). Removal of the C20 acetate through transesterification with K_2CO_3/MeOH produced the free alcohol that was immediately esterified with the

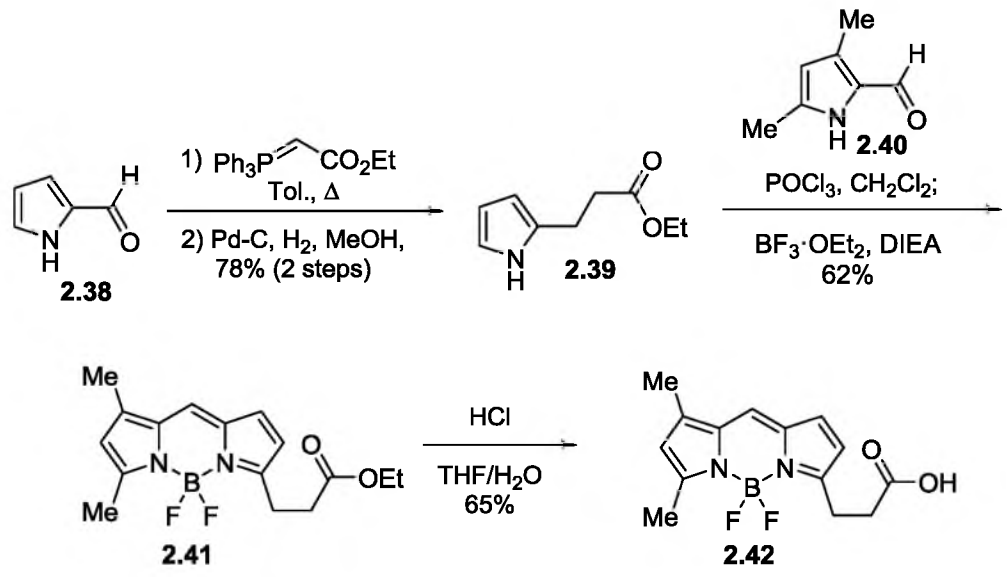
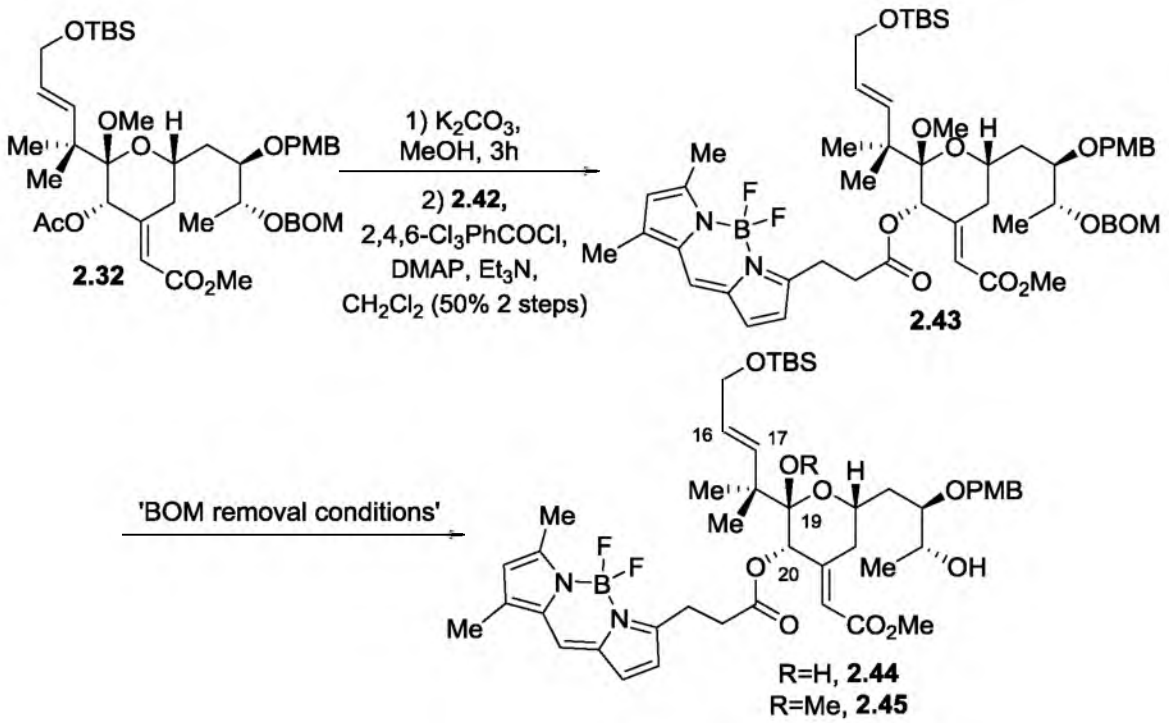


Figure 2.18. BODIPY FL Ester Synthesis



Conditions	Results
$LiBF_4$	decomposition
H_2, $Pd(OH)_2$	C16-C17 reduction
1-Me-1,4-cyclohexadiene, Pd/C	C16-C17 reduction
$BF_3{\bullet}OEt_2$, DMS	C19-C20 elimination

Figure 2.19. BODIPY FL Model Study

BODIPY FL acid using Yamaguchi conditions to give the desired ester **2.43** in a 50% yield over 2 steps. Typically, the Keck group employs a global deprotection reaction using $LiBF_4$ to remove the C26 BOM ether and any ketals present in the bryostatin analog. This tagged C-ring was then evaluated to see whether it would withstand these BOM deprotection conditions.

Using $LiBF_4$ in CH_3CN/H_2O at 80°C failed to produce any of the desired product **2.44**. Other methods using hydrogenation and transfer hydrogenation did not affect the tag

and removed the BOM ether, but caused the reduction of the C16-C17 olefin. Using BF_3•OEt_2/DMS on model **2.43** resulted in elimination across the C19-C20 bond. Even though these conditions might work on an intermediate where the C19 participates in the hydrogen bond network of bryostatin, it was deemed too risky and an alternative approach to install the BODIPY tag was assessed.

Realizing that the BODIPY FL tag needed to be installed in the last step, we began to investigate an alternative reaction to esterification. A'click reaction' was thought to be the best way to install the BODIPY tag because these conditions are generally very selective, high yielding, and simple to perform.[20] One of the most efficient 'click reactions' to date is the copper-catalyzed azide-alkyne cycloaddition. It was decided this reaction would be the best way to install the fluorescent side chain on an advanced substrate containing a plethora of different functional groups (Figure **2.20**).

Azide **2.47** was synthesized following a procedure found in the literature (Figure **2.21**, part **A**).[21] Reduction of ethyl ester **2.39** with LAH afforded the desired primary alcohol **2.48**. The alcohol was then mesylated and subsequently displaced with sodium azide in DMF to give the azide intermediate. This compound was found to be unstable to column chromatography, so the crude reaction mixture was used in the next step. Pyrrole **2.40** and **2.49** were condensed using $POCl_3$, and then treated with BF_3•OEt_2 providing BODIPY FL azide **2.47** in one pot with a 55% yield over 3 steps.

With the azide in hand, a suitable model for the click reaction was constructed (Figure **2.21**, part **B**). Removal of the C20 acetate with K_2CO_3/MeOH gave the free alcohol, which was immediately esterified with commercially available 5-hexynoic acid under Yamaguchi conditions to give the desired ester **2.50**. The Cu(I) catalyzed [2+3]-dipolar

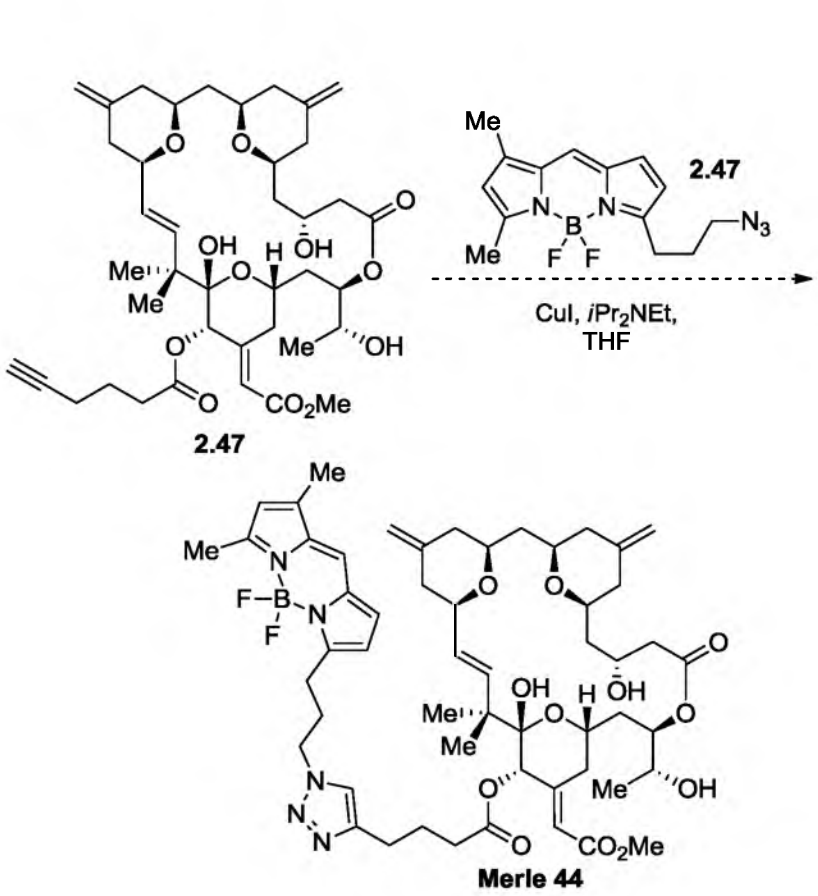


Figure 2.20. Click Reaction as a Possible Alternative to Esterification

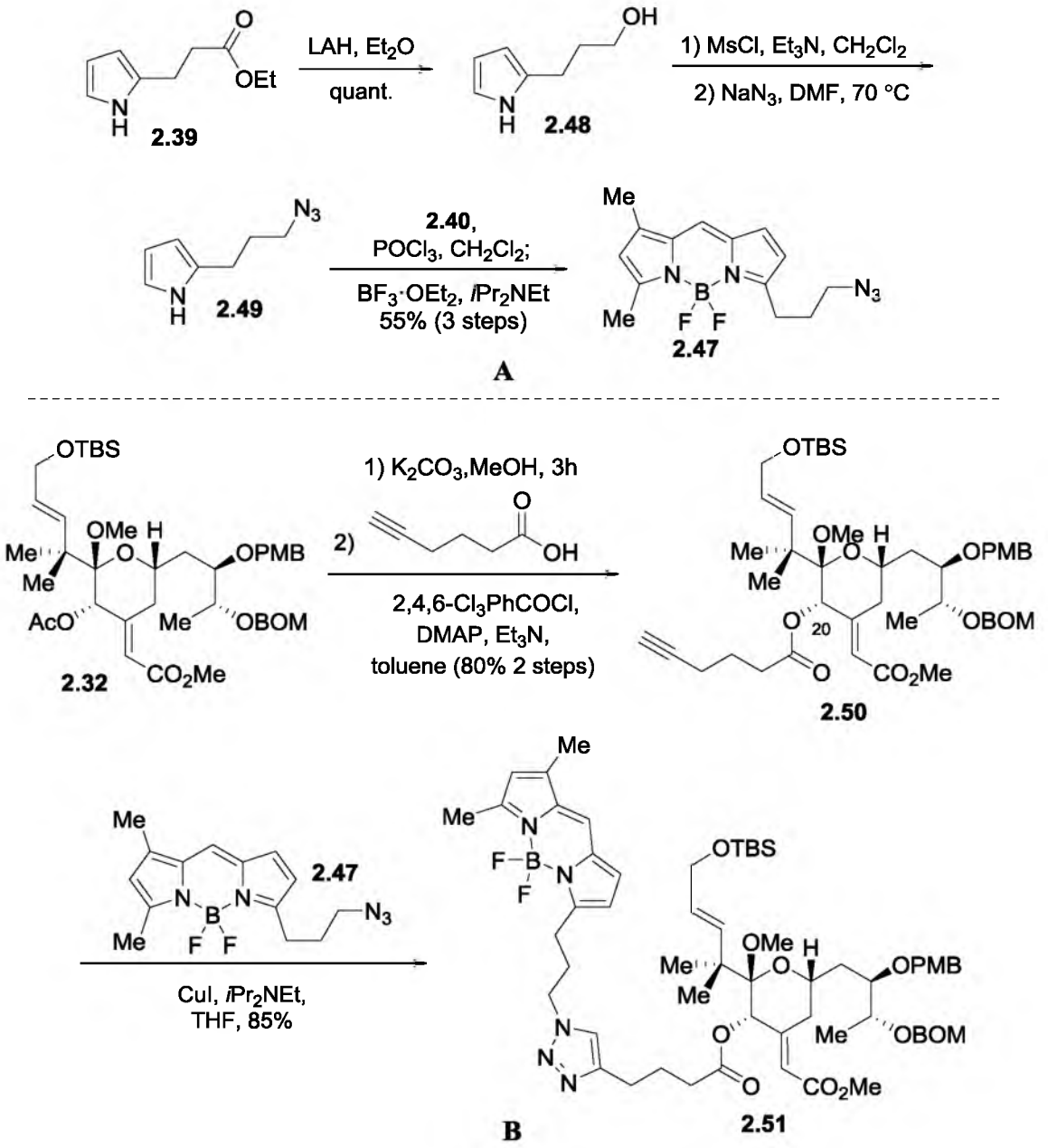


Figure 2.21. Synthesis of BODIPY FL Azide (A) and Model Study of the Click Reaction (B)

cycloaddition between this alkyne and azide **2.47** worked smoothly to give the desired triazole **2.51** as the only observable product in an 85% yield. With these results, incorporating the BODPY FL tag would now be attempted as the final step in the synthesis of Merle 44.

The Completion of Merle 44

Confident in the installation of the BODIPY tag through a click reaction, the C20 acetate was removed and the resultant alcohol was esterified with 5-hexynoic acid to give the desired ester **2.52** (Figure **2.22**). The removal of this acetate took 1 h on the macrolactone versus 3 h on C-ring **2.32**. The PMB ether was removed, and global deprotection gave bryopyran **2.46**. Stirring this alkyne with azide **2.47** in the presence of copper(I) iodide afforded desired triazole or Merle 44 in an 80% yield.

Synthesis of Merle 45: The Installation of the β-hydroxyallyl Silane

The pyran annulation has been successfully used to construct bryostatin natural products and many bryostatin analogs. The joining of the C-ring and A-ring though this reaction can be approached from 2 different directions to form the B-ring. The first approach is comprised of the A-ring as the aldehyde and the C-ring as the β-hydroxyallyl silane. Previous research on a late stage installation of a β-hydroxyallyl silane on the C-ring is shown in Figure **2.23**, part **A**. While constructing a bryostatin like tricyclic macrolactone, Dr. Truong found that a CAA reaction could be conducted on advanced C-ring enal **2.17** using a large excess of the BITIP reagent to give β-hydroxyallyl silane **2.15**.[22] This reaction was later found to have poor reproducibility, so an alternative route

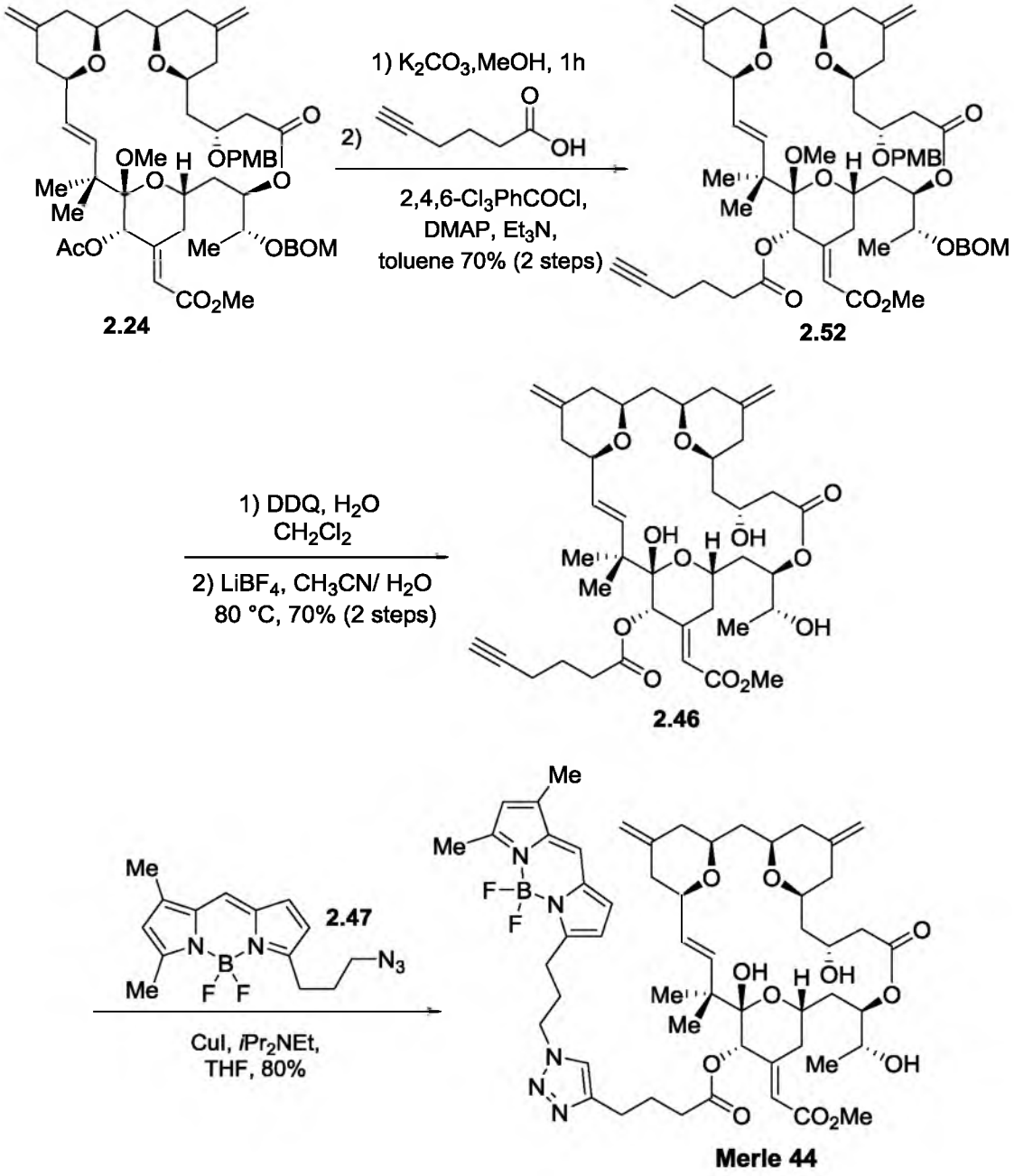


Figure 2.22. Synthesis of Merle 44

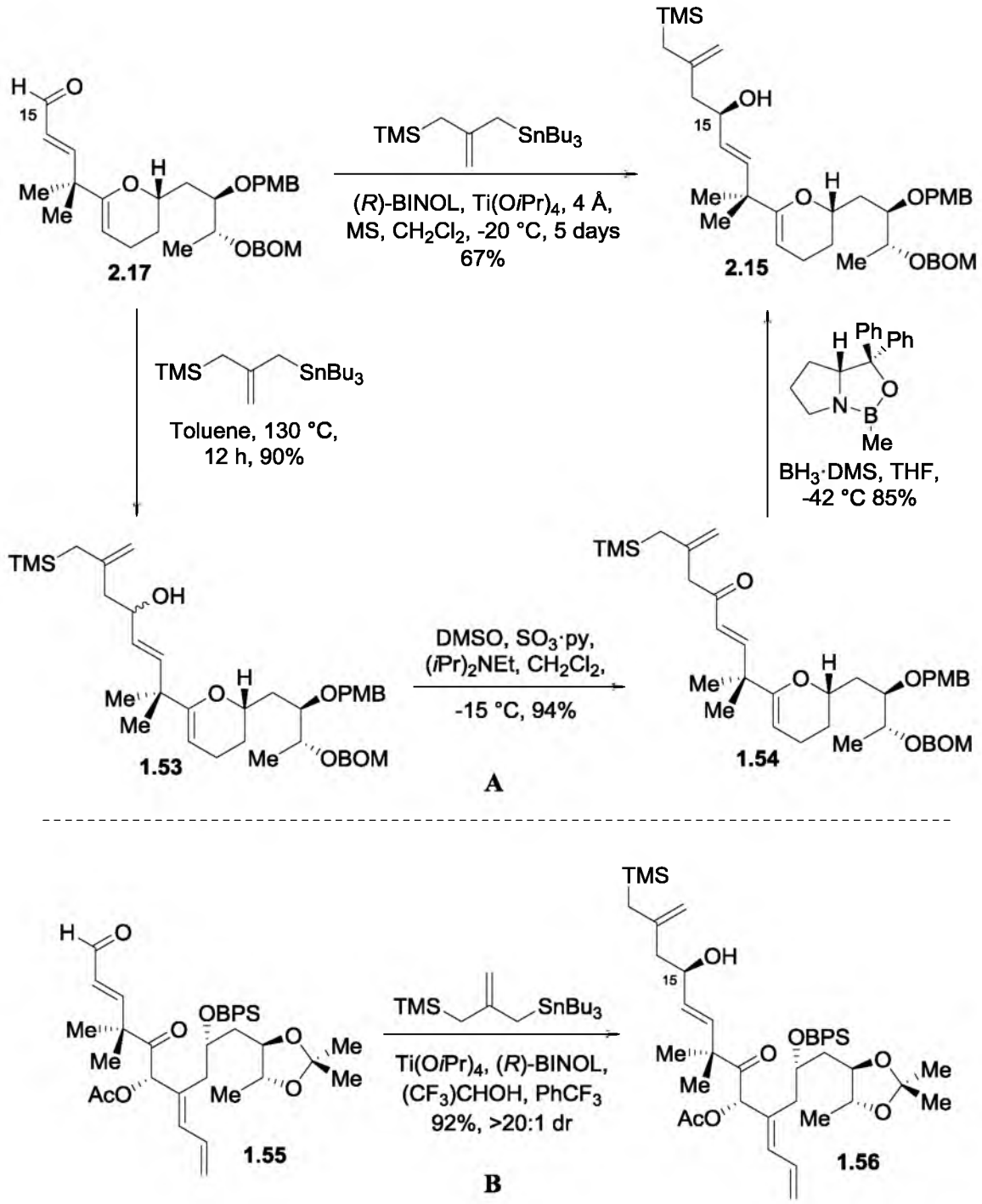


Figure 2.23. Three Step Procedure (A) and a One Step Sequence to Install the β-hydroxyallyl Silane (B)

was developed. A 3 step procedure was established using the thermal addition of trimethyl(2-((tributylstannyl)methyl)allyl)silane, a Parikh-Doering oxidation, and a Corey-Bakshi-Shibata (CBS) reduction to give β-hydroxyallyl silane **2.15** as a single diastereoisomer.[13] Another example of installing the β-hydroxyallyl silane on an advanced intermediate was done by the Krische group during the synthesis of bryostatin 7 (Figure **2.23**, part **B**).[23] A modified Keck asymmetric allylation reaction gave the C15 β-hydroxyallyl silane **2.56** as a single diastereomer.[24] This reaction was impressive since the substrate is highly oxygenated and did not affect the catalyst by competitive binding.

A potential retrosynthetic plan of fluorescent Merle 28 or Merle 45 uses a C-ring β-hydroxyallyl silane (Figure **2.24)**. When fully functionalized C-ring **2.25** was subjected to five equivalents of (*R*)-BITIP catalyst, no reaction was observed even with prolonged time. Also, subjecting cyclic **2.25** to the same conditions that the Krische group used on their acyclic C-ring was unsuccessful in producing β-hydroxyallyl silane **2.58**.

In 1986, the Corey group developed (*R*,*R*)- and (*S*,*S*)-1,2-diamino-1,2-diphenylethane *N*,*N*-sulfonamides as effective chiral auxiliaries for aldol, Diels-Alder, and allylation reactions.[25] Dr. Williams and his group at Indiana University recognized that these ligands can be reacted with boron tribromide to form a bromoborane intermediate that can be transmetalated with a variety of allylic stannanes to form chiral allyldiazaborolidines with a high degree of functional group compatibility.[26] Various papers have reported using chiral allyldiazaborolidines in asymmetric allylations reactions of complex aldehydes to form allylic alcohols[27], and used them en route to complex natural products.[28] Applying Williams' allylation conditions (Figure **2.24**) to enal **2.25** using chiral allyldiazaborolidine **2.60** produced homoallylic alcohol **2.58** in an 87% yield.

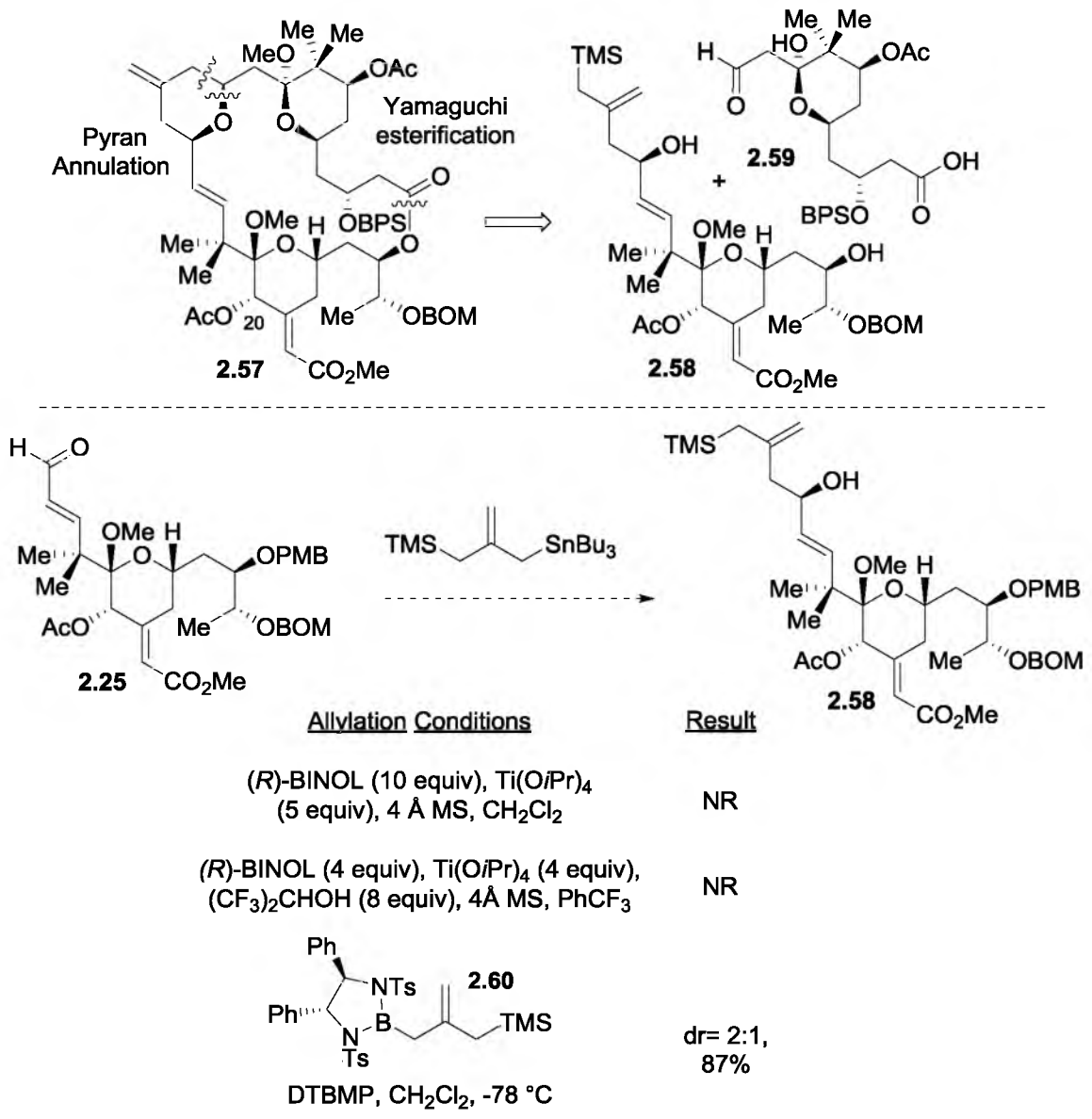


Figure 2.24. Asymmetric Allylation Conditions

Unfortunately, multiple experiments showed that the diastereomeric ratio was 2:1 by NMR and could not be improved using these conditions.

The second approach to the pyran annulation is comprised of the A-ring as the β-hydroxyallyl silane and the C-ring as the aldehyde. Examples of previous attempts to install the β-hydroxyallyl silane late stage are shown in Figure **2.25**. As with the C-ring, attempted installation of the C11 homoallylic alcohol through an asymmetric allylation reaction using (*S*)-BITIP failed to produce **2.63**.[29] Lewis acid mediated allylations of aldehyde **2.16** were attempted, but were met with limited success.[29-30] Once again, a 3 step procedure to produce β-hydroxyallyl silane **2.63** was developed, starting with the thermal addition of trimethyl(2-((tributylstannyl)methyl)allyl)silane and a Parikh-Doering oxidation of aldehyde **2.16** to give ketone **2.62**. After an evaluation of many different reduction conditions, it was found that Luche conditions provided **2.63** in an 82% yield as a 4:1 mixture of diastereomers; this reflects the stereoselectivity of the Luche reduction.[31] Another attempt to incorporate the β-hydroxyallyl silane late stage was done by Dr. Truong. It was found that using an excess of (*S*)-BITIP did in fact produce some product **2.65**, but this reaction could never be improved from a 20% yield.[32]

A potential retrosynthetic analysis of Merle 45, which has the A-ring as the β-hydroxyallyl silane, is shown in Figure **2.26**. Subjecting A-ring **2.16** to five equivalents of (*R*)-BITIP catalyst or to Krische's modified allylation conditions failed to produce any homoallylic alcohol **2.63**. Fortunately, allyldiazaborolidine **2.68** successfully added into aldehyde **2.16** provides homoallylic alcohol **2.63** in an 87% yield and as a 10:1 mixture of diastereomers by NMR. It was confirmed that the major diastereomer possessed the desired stereochemistry at C11 by comparison to a previously published compound.[31] The

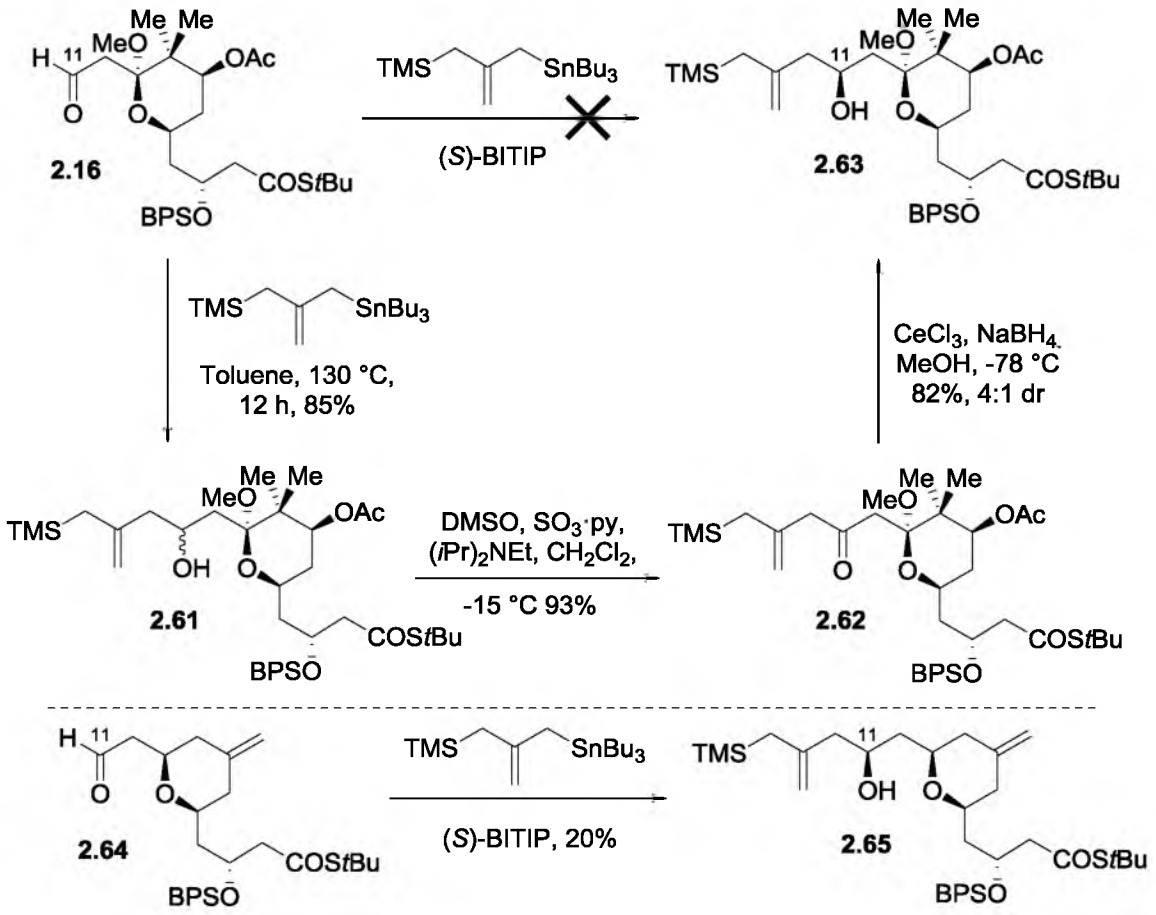
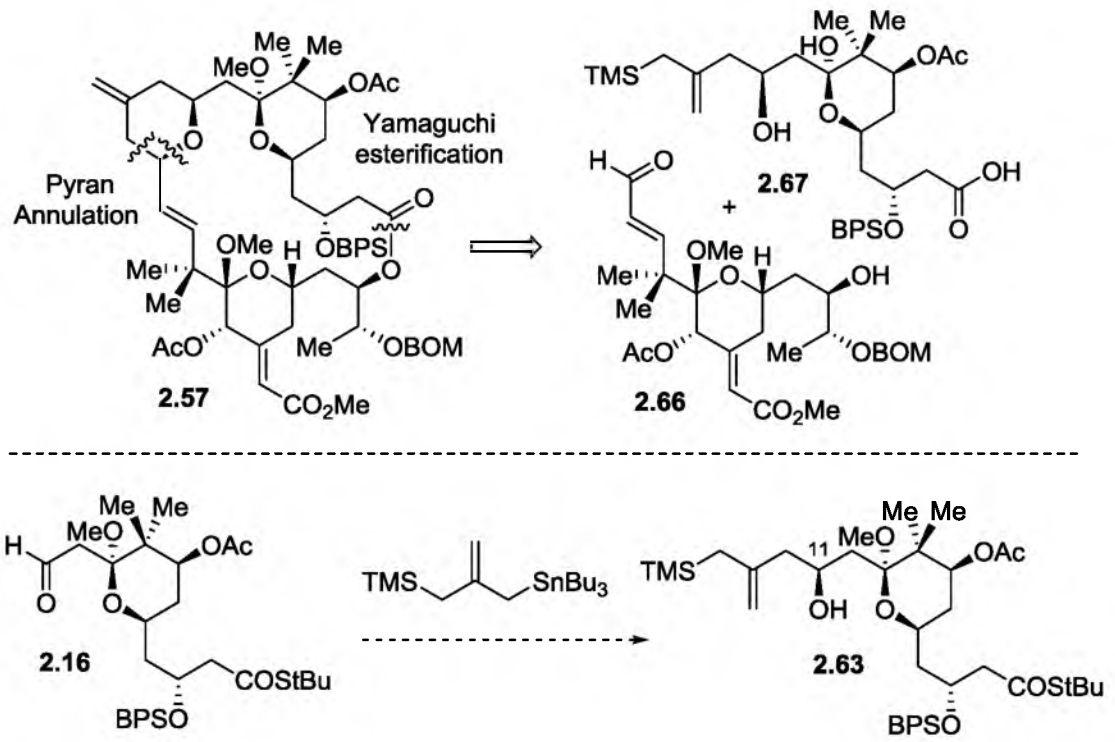


Figure 2.25. Late Stage Installation of the β-hydroxyallyl Silane on the A-ring

Williams allylation reaction procedure improves the synthesis of hydroxyallyl silane **2.63** by eliminating 2 steps and improving the diastereoselectivity for the creation of the C11 stereocenter from 4:1 to 10:1.

The Retrosynthetic Analysis of Fluorescent Merle 28 (Merle 45)

Figure **2.27** shows the retrosynthetic plan for the synthesis of Merle 45 (fluorescent Merle 28). Using the knowledge gained during the synthesis of Merle 44, the BODIPY FL tag was to be added by the selective hydrolysis of the C20 acetate, esterification, and click



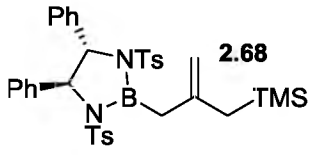
Allylation Conditions	Result
(*R*)-BINOL (10 equiv), Ti(O*i*Pr)$_4$ (5 equiv), 4 Å MS, CH_2Cl_2	NR
(*R*)-BINOL (4 equiv), Ti(O*i*Pr)$_4$ (4 equiv), $(CF_3)_2CHOH$ (8 equiv), 4Å MS, $PhCF_3$	NR
 **2.68** DTBMP, CH_2Cl_2, -78 °C	dr= 10:1, 87%

Figure 2.26. Asymmetric Allylation Conditions

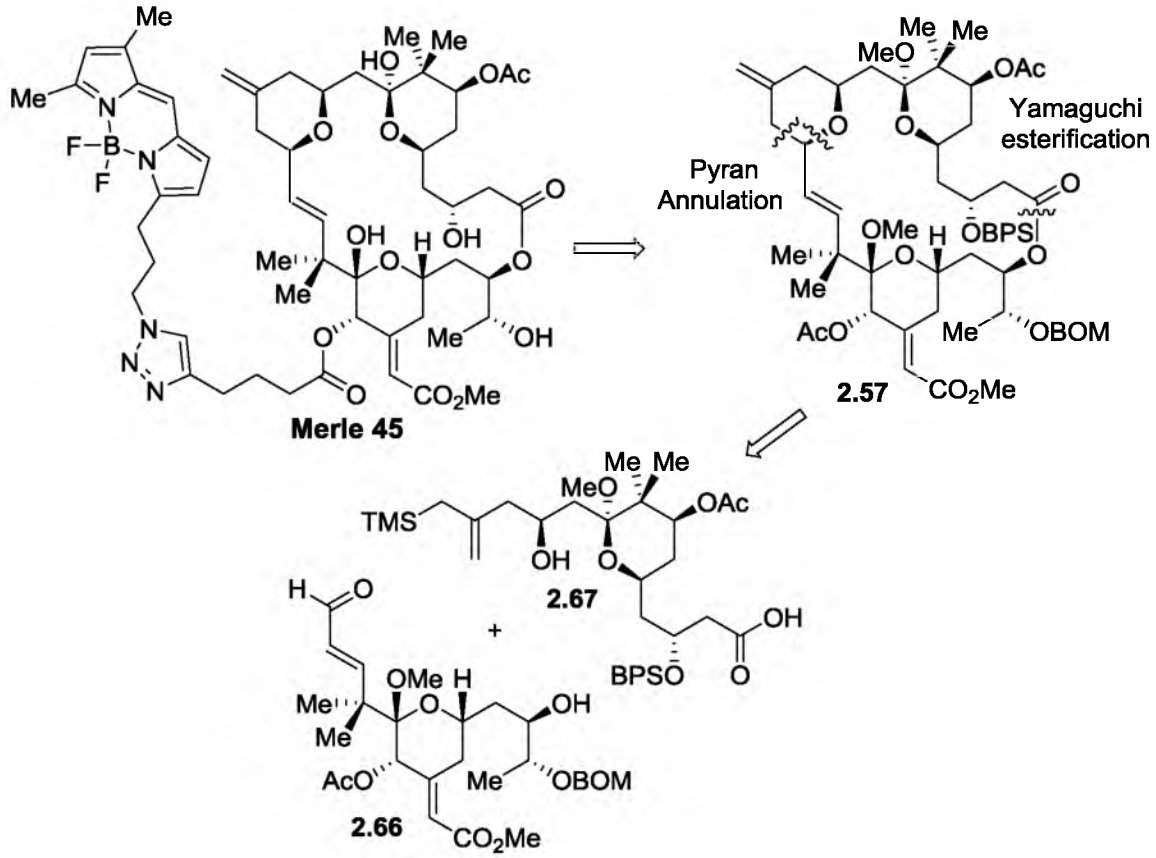


Figure 2.27. Retrosynthesis of Merle 45

reaction of intermediate **2.57**. The B-ring of **2.57** would be constructed via the pyran annulation of β-hydroxyallyl silane **2.67** and aldehyde **2.66.** The macrolactone would be completed using a Yamaguchi esterification. Again, this route improves upon the original route to Merle 28 by utilizing a fully functionalized C-ring **2.66** in the pyran annulation.

The Coupling of the A-ring and the C-ring

With both fragments, A-ring hydroxyallylsilane **2.63** and C-ring aldehyde **2.25**, in hand, these were subjected to the crucial pyran annulation conditions (Figure **2.28**). This reaction provided the tricyclic compound **2.70** in a 55% yield. A major byproduct

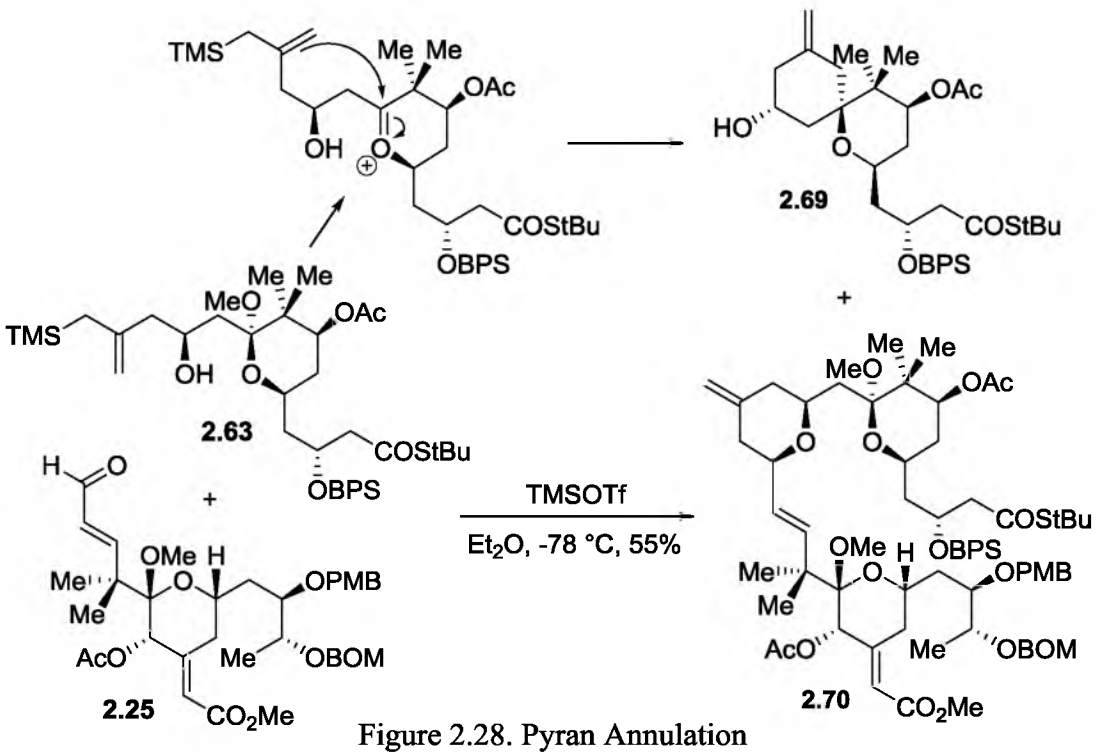


Figure 2.28. Pyran Annulation

consumed valuable A-ring **2.63** as the spirocyclic compound **2.69**. An alternative method to produce the bryopyran structure was needed because this pyran annulation reaction was low yielding and consumed a significant amount of precious A-ring material.

At this point, an intramolecular pyran annulation was investigated. In the retrosynthetic analysis shown in Figure **2.27**, this would entail performing the Yamaguchi esterification reaction first, followed by the pyran annulation. The synthesis and attempts are shown in Figure **2.29**. Subjecting the thioester **2.16** to hydrolysis using NBS gave carboxylic acid **2.71**.[33] Reacting (*S*,*S*)-allylboronate **2.68** with aldehyde **2.71** led to homoallylic alcohol **2.67** in a 77% yield as a 6:1 mixture of diastereomers. Stirring compound **2.71** with TESCl protected both the alcohol and the carboxylic acid. However, upon workup and column chromatography the TES ester was converted back to the carboxylic acid, providing **2.72**. The analytical data of this compound was found to be in

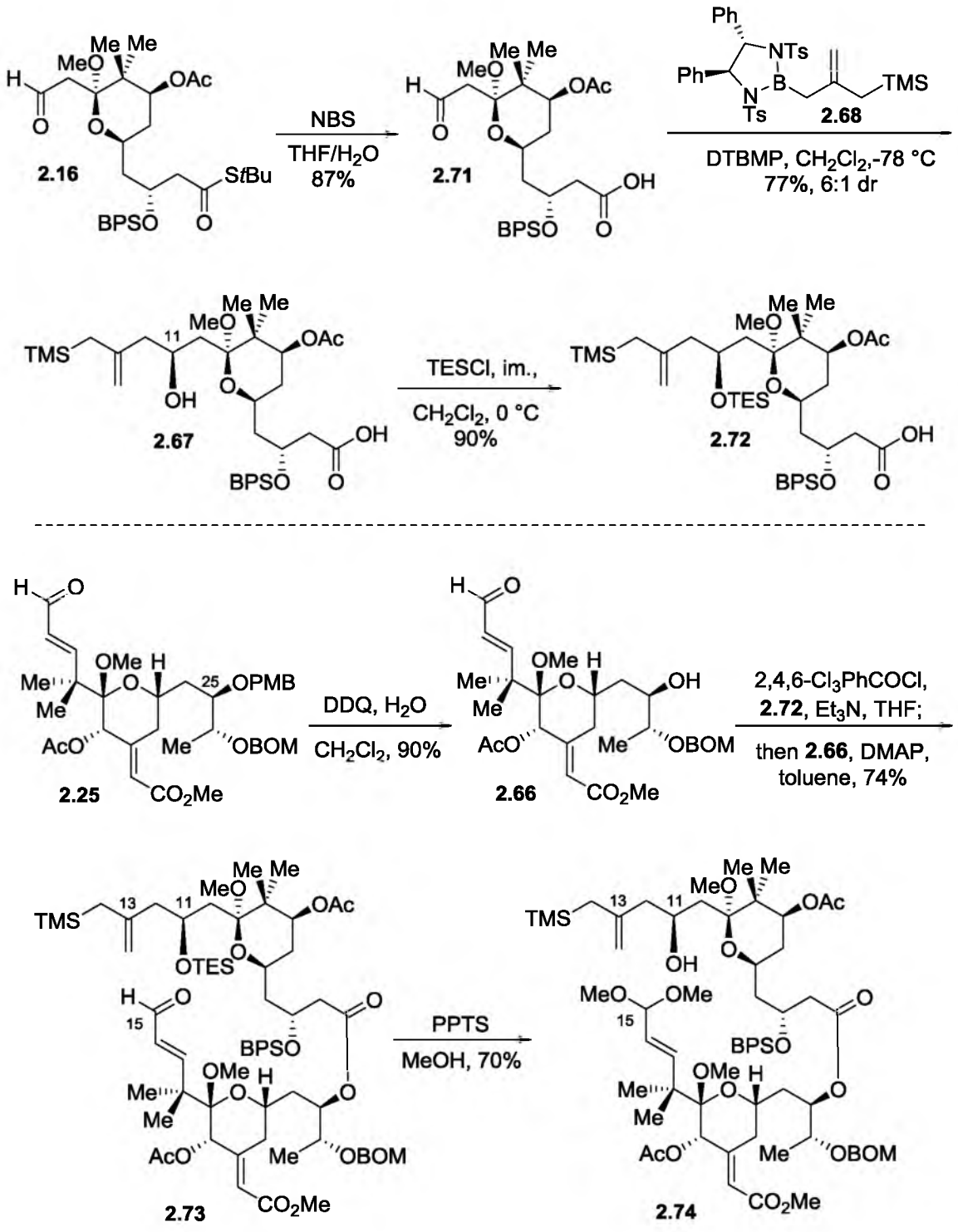


Figure 2.29. Intramolecular Pyran Annulation Reaction

agreement with the same previously published compound **2.72**.[34] The C25 PMB group was removed using DDQ, and Yamguchi esterification joined the A-ring carboxylic acid **2.72** and C-ring alcohol **2.66** to give ester **2.73** in a 74% yield. Previously developed conditions using a catalytic amount of PPTS in MeOH were found to facilitate the pyran annulation by first removing the C11 TES ether followed by cyclization to form a tricyclic macrolactone during the synthesis of bryostatin 9.[34] These same conditions were then applied to aldehyde **2.73**, but led to a different result from what was reported in the literature. The C11 TES ether was quickly removed and the C15 aldehyde was transformed into the acetal to give **2.74** as the sole product. No desired product from the macrocyclization was observed.

The pyran annulation reaction developed by the Wender group is shown in Figure **2.30**. When comparing compounds **2.29** and **2.73**, there are only 3 functional differences. There is an acetate versus a butyrate at the C20 and BOM ether versus TBS ether at the C26 position. Additionally, the C19 exists as the hemiketal versus the methyl ketal. The C20 and C26 differences were thought to be minor changes that would not have any effect on the pyran annulation. The C19 alcohol was thought to have the most influence on this reaction since it might play a role in intamolecular hydrogen bonding.

The synthesis of the hemiketal substrate started with the removal of the PMB ether with DDQ and the methyl ketal using aqueous hydrofluoric acid to provide alcohol **2.77**. Yamaguchi esterification of this alcohol and acid **2.72** produced ester **2.78** in an 82% yield. Subjecting this aldehyde to PPTS in MeOH overnight, macrocyclization occurred to give tricyclic macrolactone **2.79** in an 80% yield. It should be noted that no spirocyclic side product was observed in this reaction, improving the efficiency of the pyran annulation.

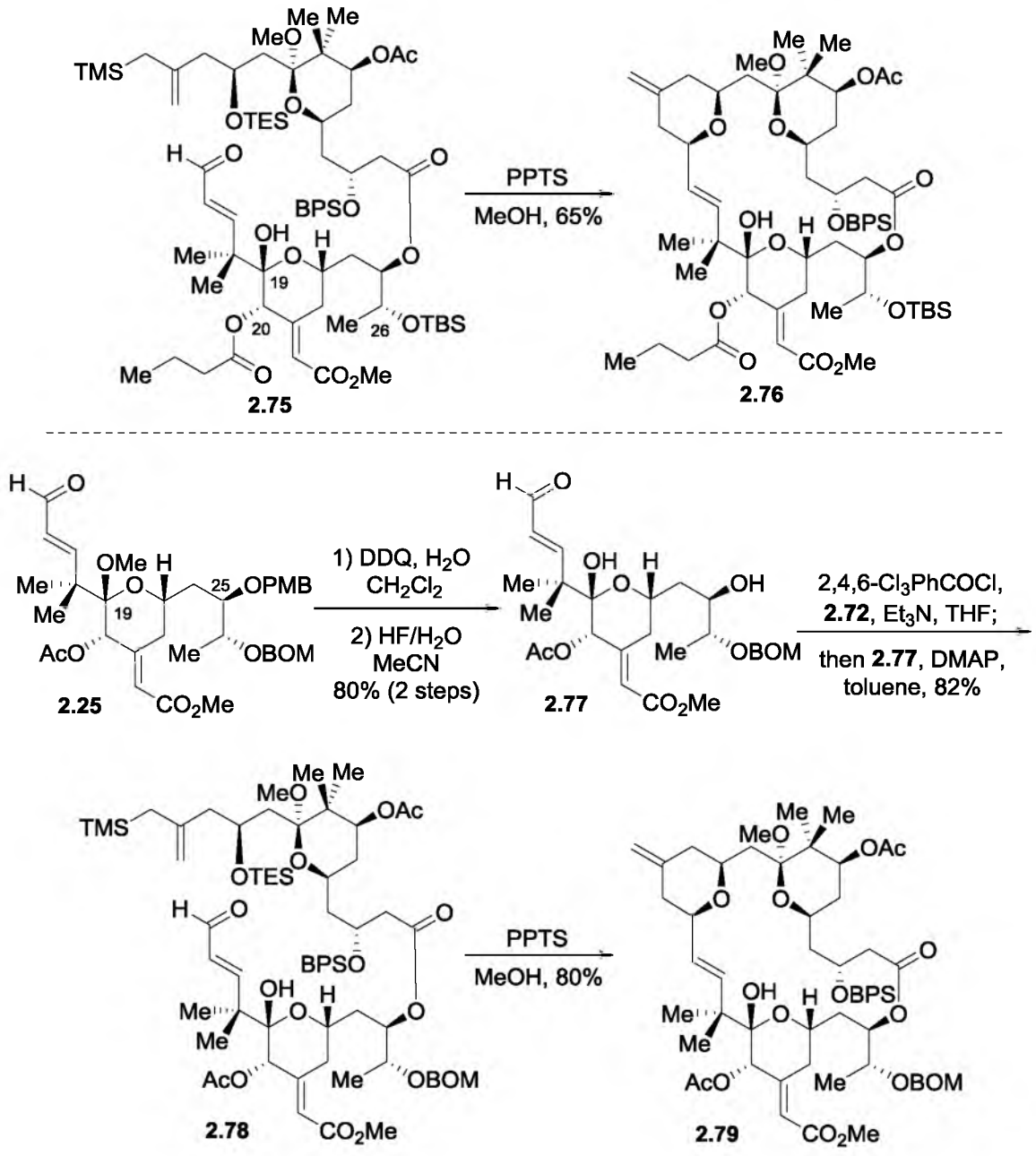


Figure 2.30. Wender's Pyran Annulation and 2nd Attempt

The necessity of the C19 alcohol is not fully understood, but it has shown to be crucial for the PPTS driven pyran annulation reaction. We suggest that the presence of this group establishes the requisite reaction conformations of the substrate (i.e., those that place the hydroxy allylsilane and the C15 aldehyde groups in spatial proximity to each other) by internal H-bonding, most likely to the C3 oxygen as is observed in the bryostatin internal H-bonding array.

The Completion of Merle 45

At this point, the alkyne needed to be introduced through hydrolysis and esterification. Dr. Poudel found when subjecting bisacetate **2.80** to K_2CO_3/MeOH, a selective methanolysis of the C20 acetate in the presence of the C7 acetate occurred in just 45 min. It was immediately esterified with (2*E*,4*E*)-octa-2,4-dienoic anhydride providing protected bryostatin 1 **2.81** (Figure **2.31**). Applying these conditions using K_2CO_3/MeOH to the C19 hemiketal **2.79**, followed by esterification with 5-hexynoic acid using Yamaguchi conditions failed to produce any of the desired product **2.80**. The reaction resulted in a single spot with the same R_f value to the starting material but, when analyzed by NMR it was a complex mixture of multiple products. The instability of intermediate **2.79** was attributed to the C19 methyl ketal not being present in the molecule. Since the hydrolysis and esterification of the C20 was unsuccessful, an alternative route towards alkyne **2.80** was sought.

To circumvent this problem, an installation of the alkyne chain before pyran annulation was planned. The synthesis of macrolactone with the 5-hexynoate side chain is shown in Figure **2.32**. Removal of TBS ether with HF•py gave allylic alcohol **2.81.** The

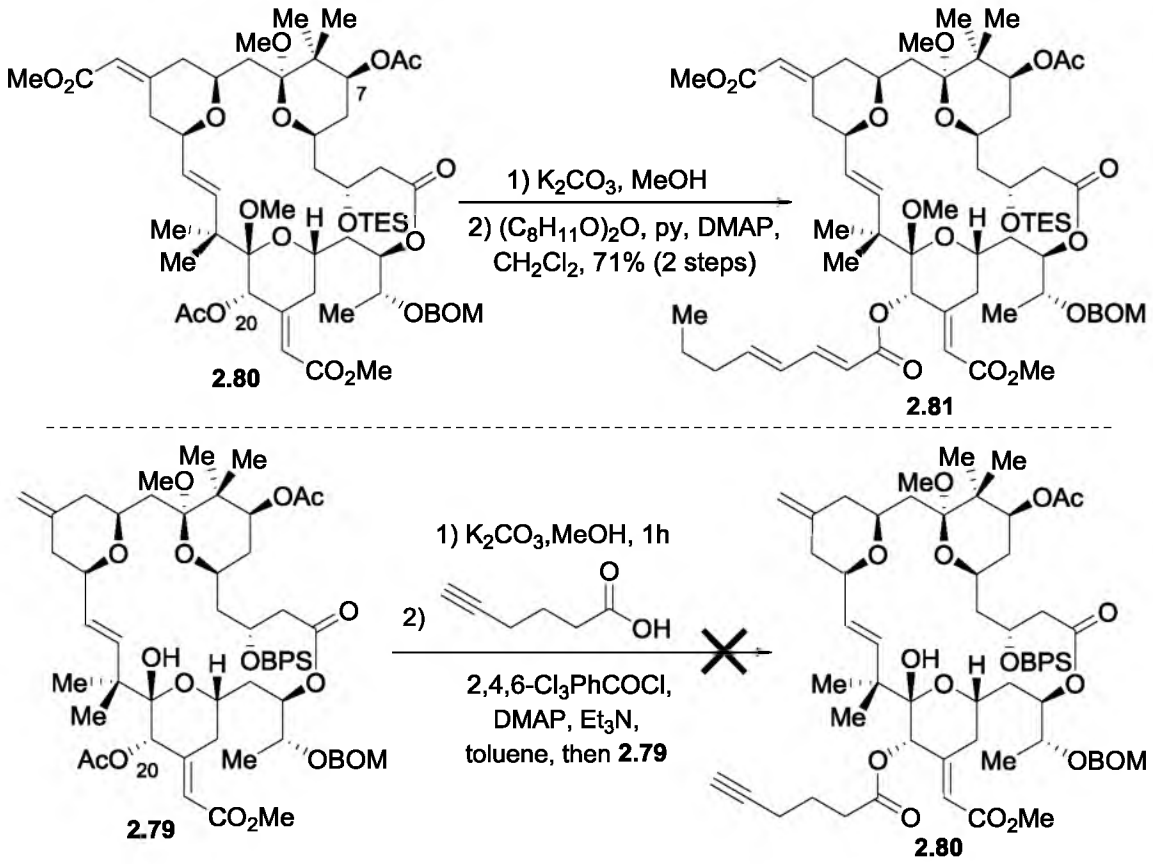


Figure 2.31. Selective Hydrolysis of the C20 Acetate

unmasked alcohol was oxidized and the C25 PMB was deprotected to produce enal **2.82**. The C19 methyl ketal was removed with aqueous hydrofluoric acid, and then coupled to carboxylic acid **2.72** using a Yamaguchi esterification to provide ester **2.83** in a 70% yield over 2 steps. A PPTS mediated pyran annulation macrocyclization of **2.83** delivered tricyclic macrolactone **2.80** in a 70% yield. With the route to protected alkyne firmly established, Merle 45 would be completed by the deprotection and installation of the BODIPY tag (Figure **2.33**). This started with a prolonged exposure of BPS ether **2.80** to HF•py followed by a global deprotection using $LiBF_4$ to give alcohol **2.84** in a 66% yield over 2 steps. Stirring this alkyne with azide **2.48** in the presence of copper(I) iodide and

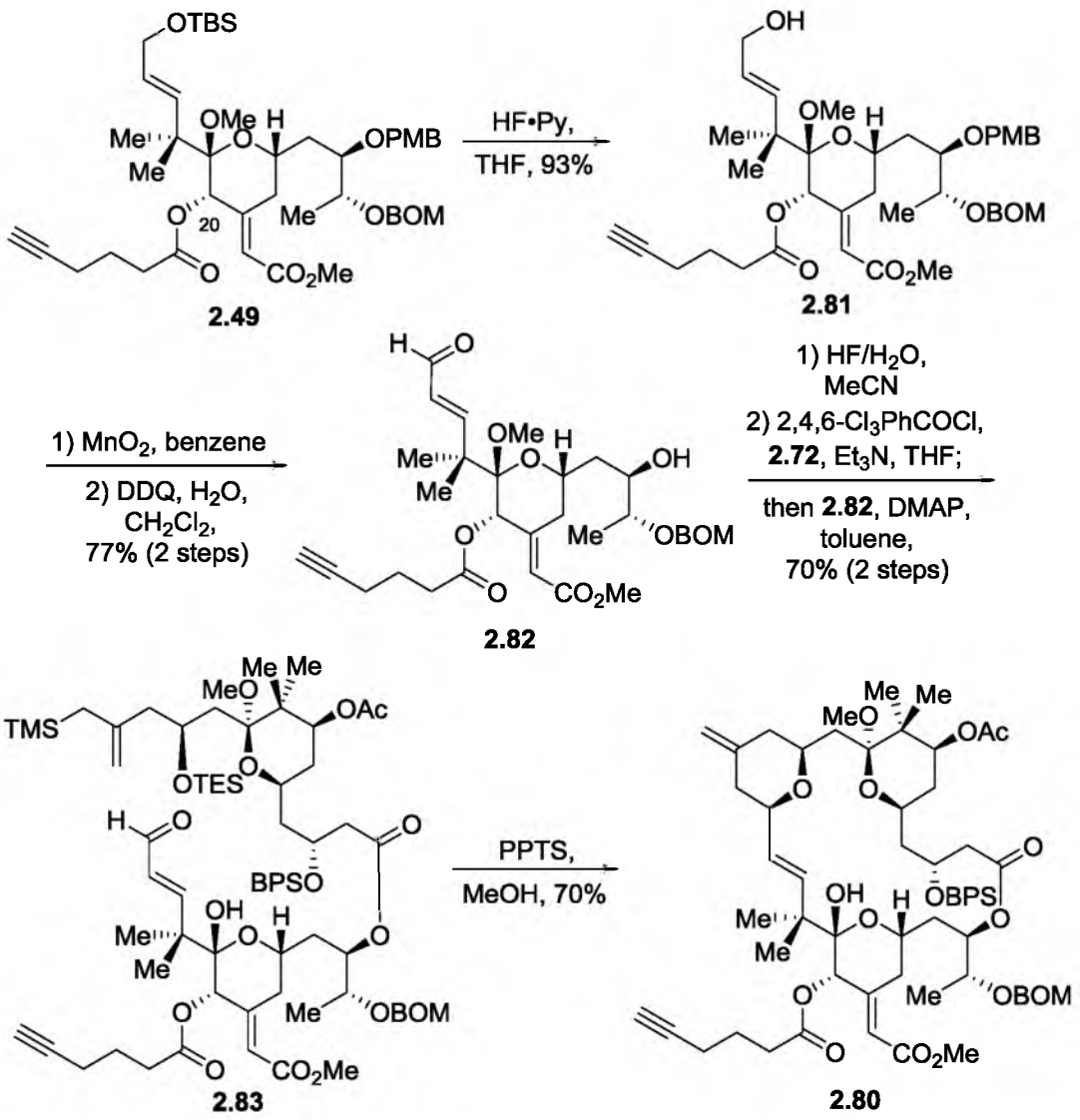


Figure 2.32. Synthesis of Macrolactone **2.80**

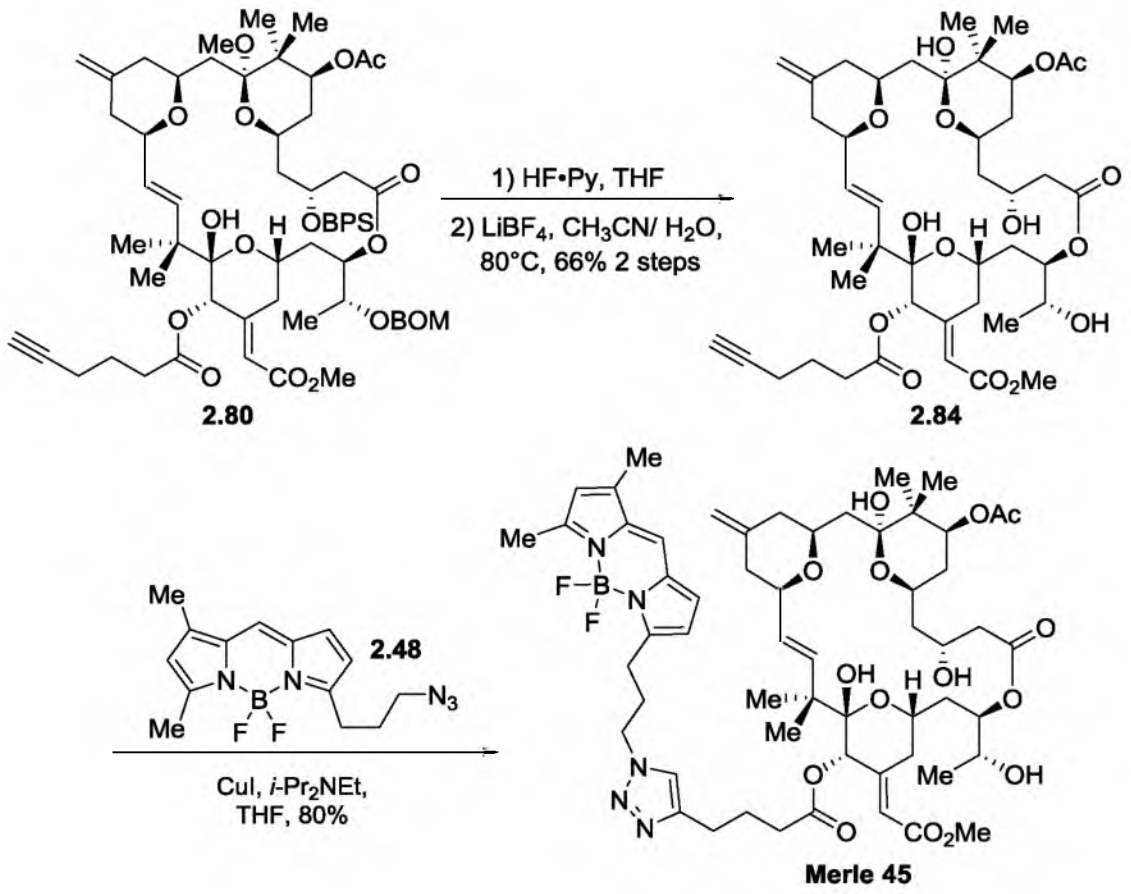


Figure 2.33. Synthesis of Merle 45

(iPr)$_2$NEt afforded the desired triazole or Merle 45 in an 80% yield.

Binding Affinity of Merle 44 and Merle 45

The determination of binding affinity was accomplished by a competitive binding assay of the ligand with the bound PDBu from isozyme PKCα. The values are an average of 3 experiments. Merle 44 was found to have a K_i of 0.64 ± 0.08, which was essentially the same as that for Merle 23 (K_i = 0.70 ±0.01 nM). Merle 45 was found to have a K_i of 0.32 ± 0.03, which was also similar to the binding affinity of Merle 28 (K_i = 0.52 ± 0.06 nM). Both Merle 44 and Merle 45 had a similar K_i value for PKCα as does bryostatin 1 (K_i

= 0.43 ± 0.03 nM)

Evaluation of Merle 44 and Merle 45 in Toledo Cells

In Toledo cells, also known as human non-Hodgkin cells, bryostatin 1 (IC_{50} = 0.091 ± 0.026 nM) and PMA (IC_{50} = 0.565 ± 0.272 nM) behave similarly causing apoptosis of Toledo cells at low concentrations. Both Merle 23 (IC_{50}= 0.331 ± 0.105 nM) and Merle 28 (IC_{50} = 0.111 ± 0.009 nM) also cause apoptosis at low concentrations. Merle 44 and Merle 45 were assayed in these cells to evaluate the potency of these analogs compared to PMA, bryostatin 1, Merle 23, and Merle 28 (Figure **2.34**). Merle 45 (IC_{50}= 0.334 ± 0.068 nM) was found to have similar inhibitory concentrations as PMA, bryostatin 1, and Merle 28 in the Toledo cells. Merle 44 (IC_{50} = 3.168 ± 0.672 nM) was the least potent of the group showing about a 10 fold decrease in potency from Merle 23. Nonetheless, this study showed that despite the incorporation of the large and complex C20 side chain, both Merle 44 and Merle 45 were functional in living cells. This was a major relief as there was no guarantee that this would be the case.

Proliferation and Attachment Assays in U937 Cells

Merle 45 resembled bryostatin 1 and Merle 28 in the U937 proliferation assay by giving a dose-dependent biphasic pattern in its ability to inhibit cell growth (Figure **2.35**). Merle 45 contrasts with PMA by being far less effective in inducing apoptosis of the U937 cells. When co-administered, Merle 45 is a functional antagonist of PMA and blocks the effect of the phorbol ester (10 nM PMA+ 1000 nM Merle 45). Merle 28 and Merle 45 behave similarly in their ability to block the effect of PMA. Merle 45 also resembled

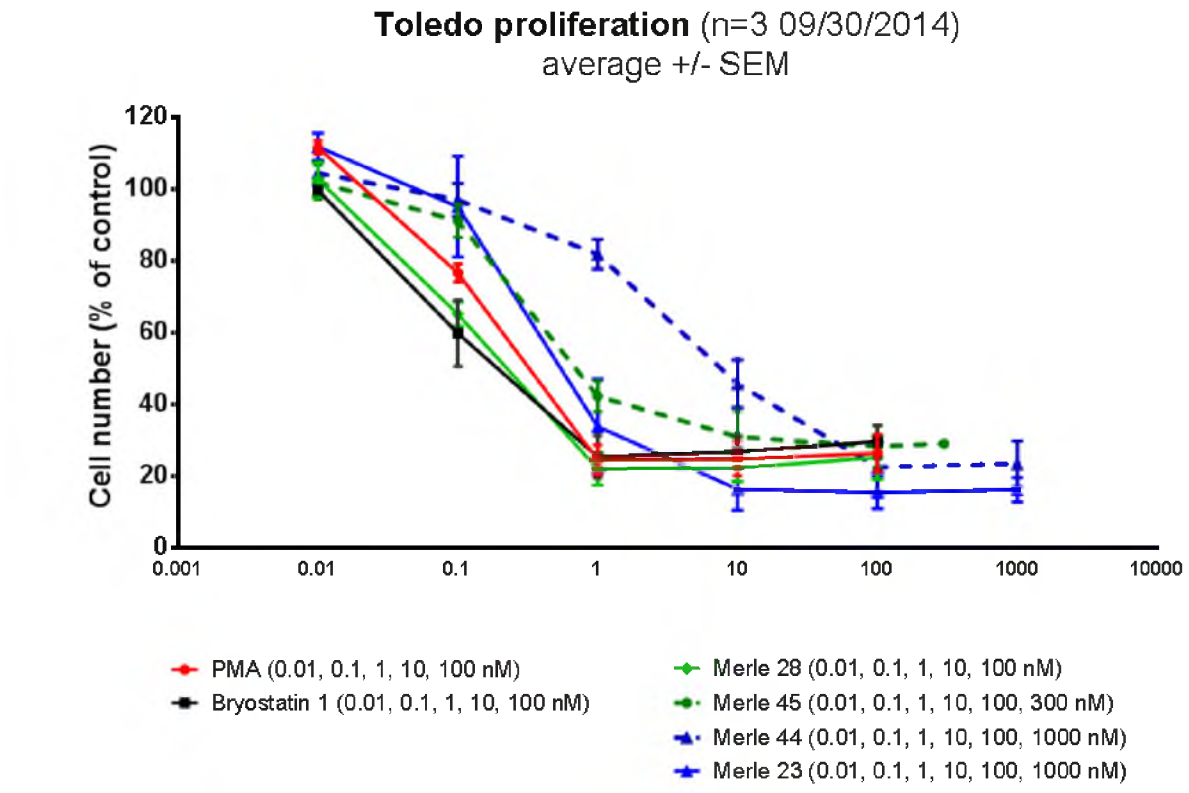


Figure 2.34. Proliferation Studies in Toledo Cells

bryostatin 1 and Merle 28 in the U937 attachment assay by showing a diminished amount of cell attachment when compared to PMA (Figure **2.36**). Interestingly, Merle 45 induces less attachment than Merle 28 resulting in a pattern that appears even more bryostatin like. The biological results with Merle 45 reveal a distinctly bryo-like pattern of behavior in U937 cells.

In contrast to Merle 45, Merle 44 resembled PMA and Merle 23 by inhibiting proliferation. Merle 44 also does not antagonize the response to PMA as does bryostatin 1. In cell attachment, Merle 44 behaves similarly to Merle 23 and PMA by inducing a significant amount of cell attachment. Both Merle 44 and Merle 45 have significant changes in the southern portion of the molecule but both retain their biological properties

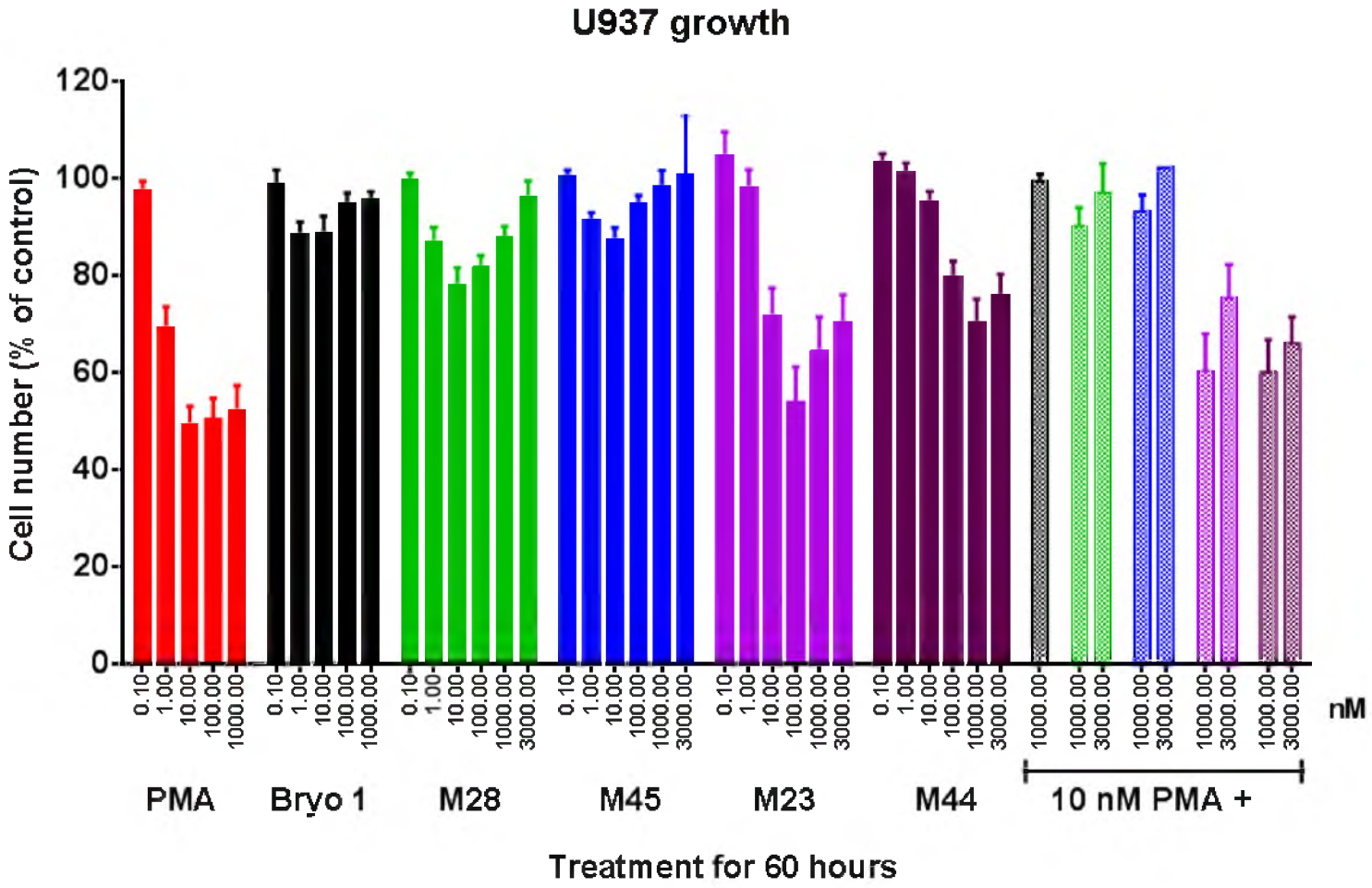


Figure 2.35. Proliferation of U937 Cells

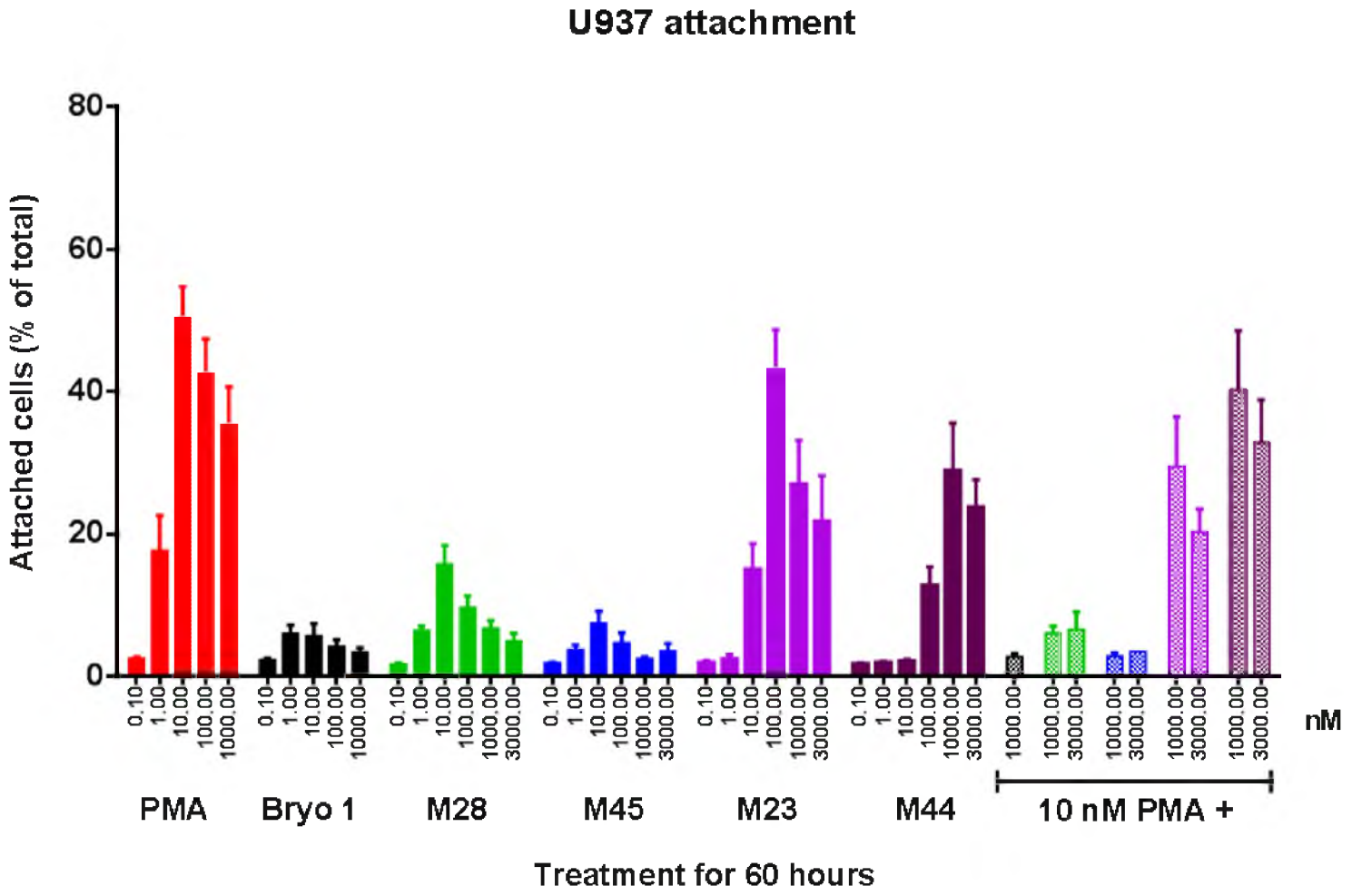


Figure 2.36. Attachment of U937 Cells

in the U937 cell line. Another interesting observation from these assays is that Merle 44 is 'PMA-like' in these assays, but is slightly more 'bryo-like' than Merle 23. This suggests that the C20 ester side chain could possibly be altered, in a Merle 23-like analog, to switch the biological response to a more 'bryo-like' compound.

TNFα Secretion Assay in U937 Cells

Another assay involving U937 cells evaluates the effect of PMA, bryostatin 1, Merle 23, Merle 44, Merle 28, and Merle 45 on the secretion of tumor necrosis factor α (Figure **2.37**). It is believed that TNFα is an important contributor in PMA's ability to induce apoptosis in U937 cells. After treatment of the U937 cells with PMA for 60 h, the ligand induces a very high level of TNFα. Merle 23, and Merle 44 also induces a high level of TNFα secretion. Merle 44 has slightly less TNFα secretion than Merle 23. Bryostatin 1, Merle 28, and Merle 45 all induced a similar levels of TNFα .

Visualization of Merle 44 and Merle 45 in LNCaP Cells

Initial studies from the Blumberg group are shown in Figure **2.38**. Red fluorescence protein (RFP)-PKCδ, and green fluorescent Merle 44 and Merle 45 are currently being evaluated using confocal microscopy in LNCaP cells for cellular uptake and localization. Both Merle 44 and Merle 45 initially reside in the internal membranes when LNCaP cells are treated with 1000 nM of the ligand after 10 min. The yellow color comes from the overlay of (RFP)-PKCδ and Merle 45. At this concentration, the drugs did not seem to colocalize with PKCδ and did not cause translocation of the enzyme. Also, initial results show a slower uptake of Merle 44 into the cells than the more polar Merle 45 (Figure **2.39**).

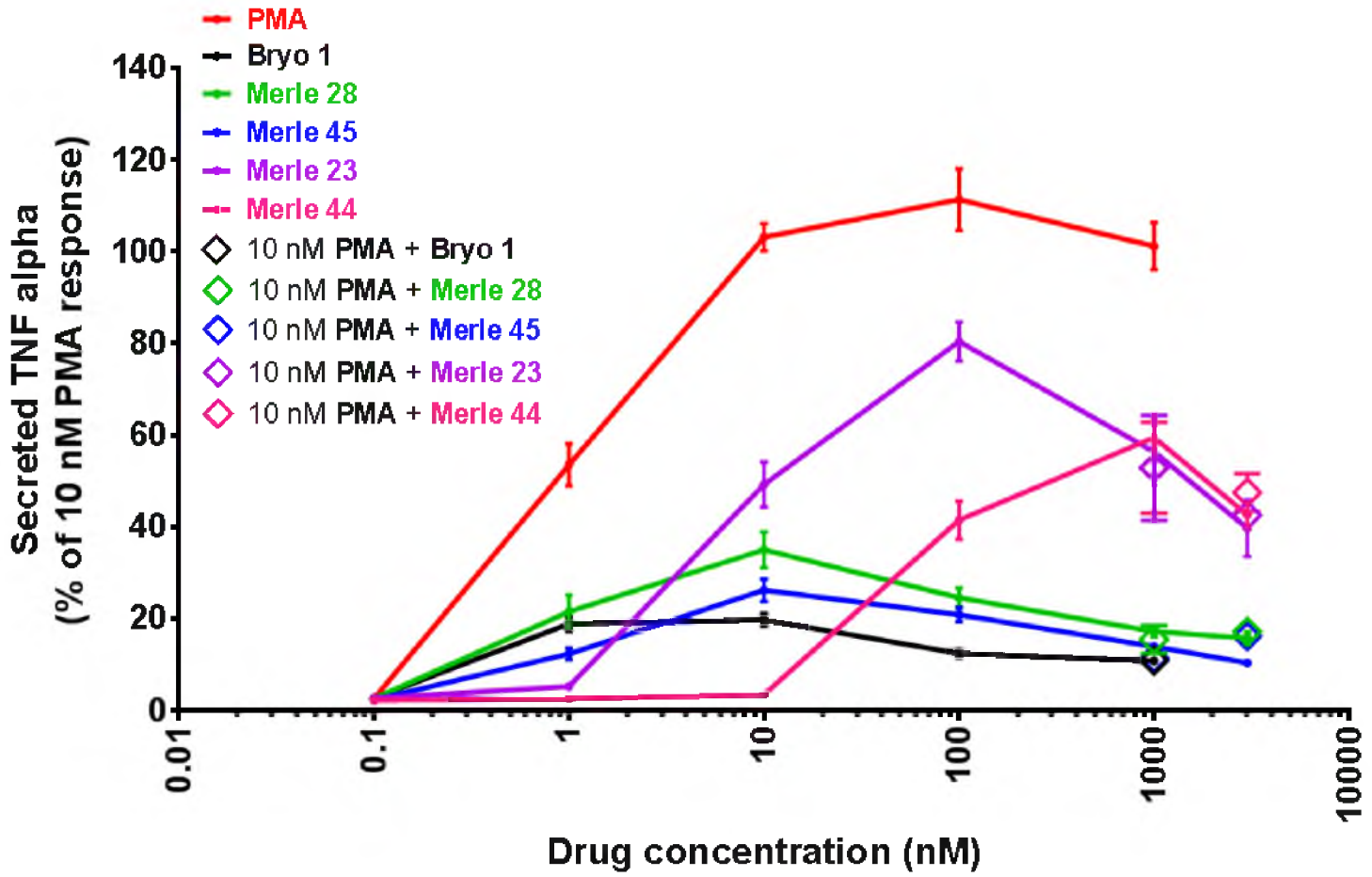


Figure 2.37. TNFα Secretion in U937 Cells

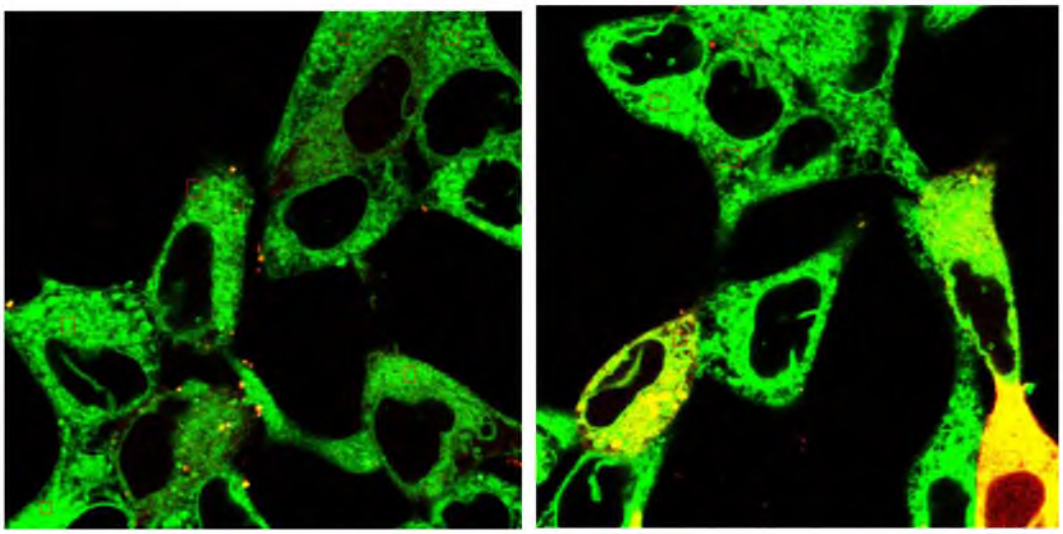


Figure 2.38. Distribution of Merle 44 (left) and Merle 45 (right)

Additional experiments are needed since these data are only from one experiment.

Conclusions

Merle 44 and Merle 45 were rapidly constructed using a fully functionalized C-ring and the pyran annulation. An investigation into installing the β-hydroxyallylsilane led to a very mild and effective way of installing this functionality at a late stage on the A-ring. A highly selective intramolecular pyran annulation using PPTS, in the presence of fully functionalized A-ring, was found to be dependent on the C19 alcohol for success. Significant changes at the C20 ester by installing the BODIPY FL tag did not have a substantial effect on the biology of the new fluorescently labeled analogs. Merle 44 was found to be a functional analog of Merle 23 and Merle 45 was found to be a functional analog of Merle 28.

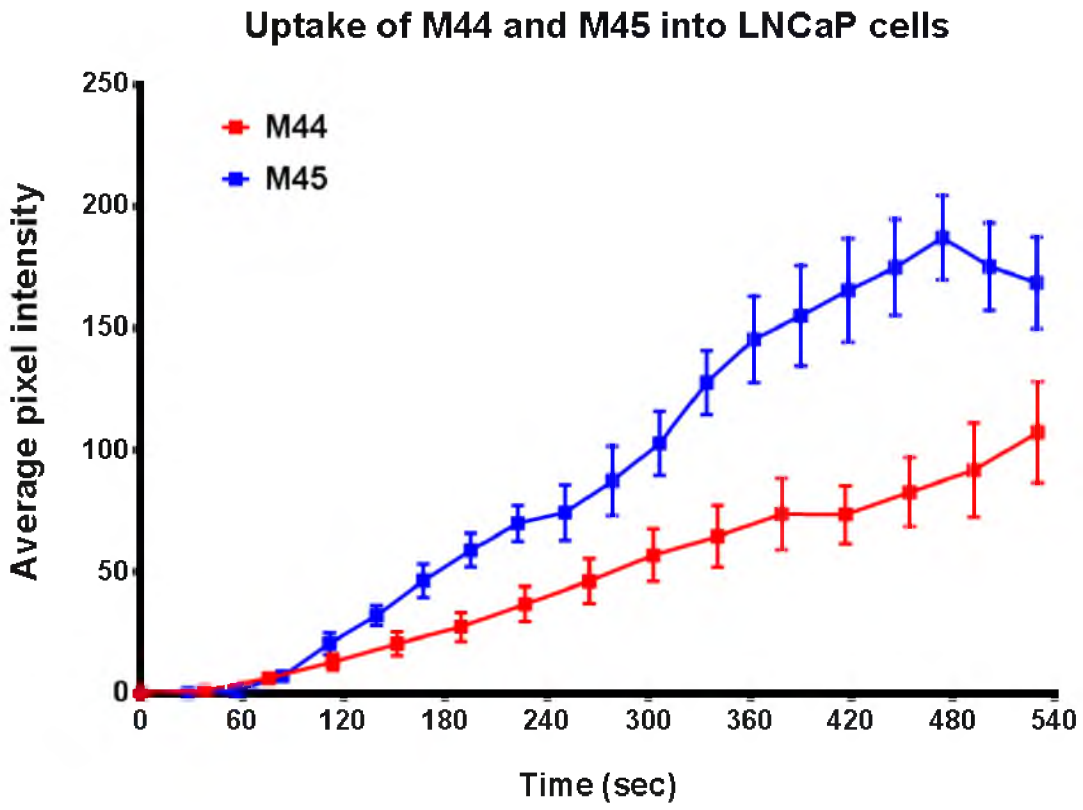


Figure 2.39. Uptake of Merle 44 and Merle 45

Future Work

Further biological studies by the Blumberg group will be conducted on Merle 44 and Merle 45. A measurement of the rate of uptake of the compounds and their distribution after uptake will be obtained using real time analysis similarly to the fluorescent phorbol ester studies (Figure **2.40**, part **A**). A comparison of their kinetics and localization will be correlated to that of PKC isoform. The PKC isoforms will be labeled with mCherry, which is a red variant of PKC isoforms. The green fluorescent bryostatin analogs can then be compared to the red fluorescent PKC localization simultaneously. A phorbol ester containing the BODIPY FL tag through a click reaction will also be constructed. With these compounds, we can also potentially measure fluorescence resonance energy transfer

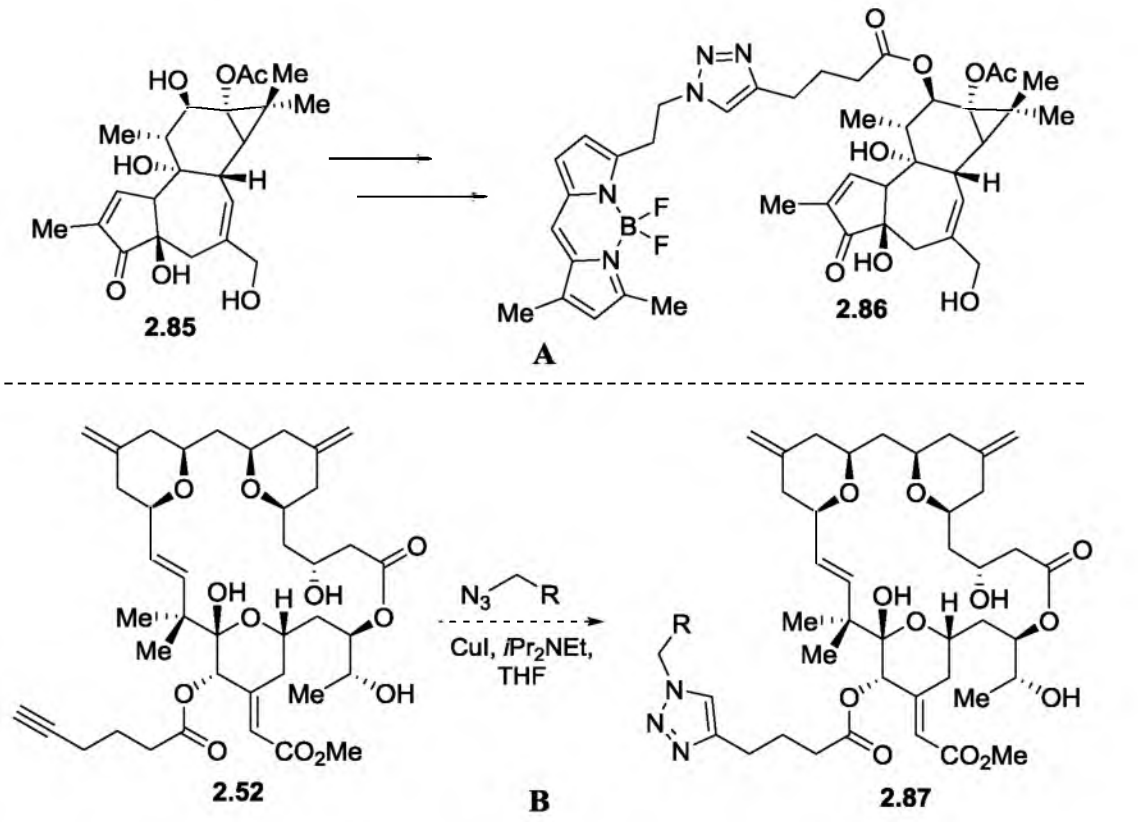


Figure 2.40. Fluorescent Phorbol Ester (A) and SAR Studies Using the Click Reaction (B)

containing the BODIPY FL tag through a click reaction will also be constructed. With these compounds, we can also potentially measure fluorescence resonance energy transfer (FRET) between the fluorescent PKC and the fluorescent ligands to see if there is a conformational difference between Merle 44, Merle 45 and the fluorescent phorbol ester **2.86**.

The results from Merle 44 also suggest that we might potentially switch a Merle 23-like analog to a bryo-like compound. This is because Merle 44 was found to be less

'PMA-like' than Merle 23. SAR studies could be conducted on the C20 side chain of Merle 23 by changing the overall polarity of the molecule (Figure **2.40**, part **B**). This could be quickly and efficiently accomplished using the click chemistry between a desired azide and alkyne **2.52**.

Experimental Section

General Experimental Procedures, Materials and Instrumentation

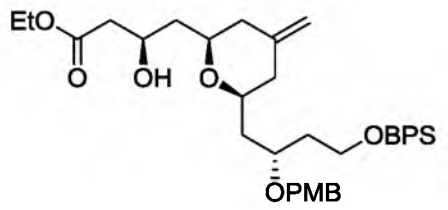
Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966).[35] $(i\text{Pr})_2\text{NH}$, $(i\text{Pr})_2\text{NEt}$, pyridine, Et_3N, EtOAc, CH_2Cl_2, and TMEDA were distilled from CaH_2. The titer of *n*-BuLi was determined by the method of Eastham and Watson[36]. Et_2O and THF were distilled from Na under an atmosphere of N_2. MeOH was distilled from dry Mg turnings. Ozone was generated using a Welsbach model T-816 generator. All other reagents were used without further purification. Yields were calculated for material judged homogenous by thin layer chromatography and nuclear magnetic resonance (NMR). Thin layer chromatography was performed on Merck Kieselgel 60 Å F_{254} plates or Silicycle 60Å F_{254} eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid, 4-anisaldehyde, or an aqueous potassium permanganate solution. Flash column chromatography was performed with Silicycle flash silica gel 40 – 63 μm, slurry packed with hexanes in glass columns. Glassware for reactions was oven dried at 125 °C and cooled under a dry nitrogen atmosphere prior to use. Liquid reagents and solvents were introduced by oven dried syringes through septum-sealed flasks under a nitrogen atmosphere. Nuclear magnetic

resonance spectra were acquired at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million relative to the signal residual $CDCl_3$ at 7.27 ppm. Chemicals shifts for carbon nuclear magnetic resonance (^{13}C NMR and DEPT) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.23 ppm. Chemical shifts of the unprotonated carbons ('C') for DEPT spectra were obtained by comparison with the ^{13}C NMR spectrum. The abbreviations s, d, apd, dd, ddd, dddd, t, td, tt, q, dq, and m stand for the resonance multiplicity singlet; doublet; apparent doublet; doublet of doublets; doublet of doublet of doublets; doublet of doublet of doublet of doublets; doublet of doublet of doublets of doublets; triplet; triplet of doublets; triplet of triplets; quartet; doublet of quartets; and multiplet, respectively. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length. Specific rotations ($[\alpha]_D^{20}$, Unit: $°cm^2/g$) are based on the equation $\alpha = (100 \cdot \alpha)/(l \cdot c)$ and are reported as unitless numbers where the concentration c is in g/100 mL and the path length l is in decimeters. Mass spectrometry was performed at the mass spectrometry facility of the Department of Chemistry at The University of Utah on a double focusing high resolution mass spectrometer. Compounds were named using ChemDraw 12.0.0.

Experimental Procedures and Analytical Data for A-ring **2.26**

The compounds **2.30**, **2.31**, and **2.26** were previously prepared by Dr. Wei Li and are reported in his Ph.D. thesis and in the literature.[6] These syntheses were repeated on a larger scale to assess these for use in the present work. Compound **2.30** was prepared using an alternative 2 step procedure to simplify its synthesis. The experimental procedure and

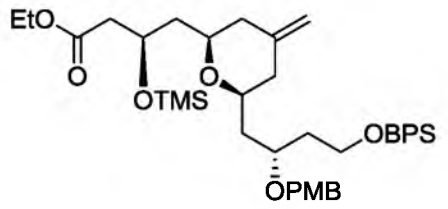
analytical data for these compounds are reproduced here for the convenience of those who may need to repeat this work.



(3*R*)-ethyl 4-(6-((*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-((4-methoxybenzyl) oxy)butyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-3-hydroxybutanoate (2.30).[6] To a stirring solution of the silyl ether **2.29** (1.35 g, 1.71 mmol, 1.0 equiv) in THF (17 mL) at 0 °C in a 60 mL plastic bottle, was added HF•py (20% in pyridine, 4.3 mL). TLC analysis after 38 h at rt indicated complete consumption of the starting material. The mixture was quenched by pipetting into a stirring mixture of saturated aqueous $NaHCO_3$ solution (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This material was carried onto the next step without further purification.

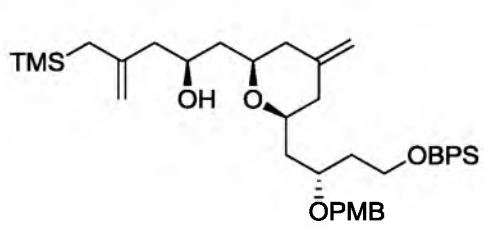
To a stirring solution of crude diol in CH_2Cl_2 (30 mL) in a 50 ml rb flask at 0 °C, was added Et_3N (0.72 mL, 5.13 mmol, 3.0 equiv) followed by BPSCl (0.44 mL, 1.71 mmol, 1.0 equiv) and DMAP (42 mg, 0.34 mmol, 0.2 equiv). The reaction was allowed to proceed for 3 h at 0 °C, then quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography

using a 3.0 × 30.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (15-30) were combined and concentrated under reduced pressure to yield alcohol **2.30** (1.02 g, 81%) as a clear oil: R_f = 0.30 (20% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.65 (m, 4H), 7.46-7.36 (m, 6H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 11.3 Hz, 2H), 4.39 (ABq, *J* = 10.9 Hz, Δν = 41.2 Hz, 2H), 4.28-4.22 (m, 1H), 4.14 (ddd, *J* = 14.2, 7.0, 2.0 Hz, 2H), 3.80 (s, 3H), 3.79-3.72 (m, 4H), 3.57-3.47 (m, 2H), 2.52 (dd, *J* = 15.5, 7.4 Hz, 1H), 2.44 (dd, *J* = 15.7, 7.5 Hz, 1H), 2.22 (d, *J* = 13.4 Hz, 1H), 2.16 (d, *J* = 13.4 Hz, 1H), 1.99 (t, *J* = 12.0 Hz, 1H), 1.92 (t, *J* = 12.0 Hz, 1H), 1.83-1.62 (m, 6H), 1.24 (t, *J* = 6.9 Hz, 3H), 1.06 (s, 9H). 125 MHz ^{13}C NMR ($CDCl_3$) δ 179.5, 152.1, 134.9, 130.6, 130.0, 129.8, 129.7, 128.6, 123.4, 118.9, 115.4, 77.5, 45.6, 43.1, 33.8, 29.3, 25.9, 24.0.



(3*R*)-ethyl 4-(6-((*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-((4-methoxybenzyl) oxy)butyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-3-((trimethylsilyl)oxy)butanoate (2.31).[6] To a stirring solution of alcohol **2.30** (940 mg, 1.26 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) in a 50 ml rb flask at 0 °C, was added Et_3N (0.53 mL, 3.78 mmol, 3.0 equiv) followed by TMSCl (0.32 mL, 2.52 mmol, 2.0 equiv). The reaction was allowed to proceed for 2 h at rt, after which time TLC analysis indicated complete consumption of the alcohol starting material. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL), the phases were separated, and the aqueous layer was extracted

with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography using a 2.0 × 25.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (4-21) were concentrated to give silyl ether **2.31** (1.02 g, 98%) as a clear oil. R_f = 0.62 (20% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.71-7.66 (m, 4H), 7.46-7.36 (m, 6H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.72 (d, *J* = 11.1 Hz, 2H), 4.42 (ABq, *J* = 10.7 Hz, Δν = 28.2 Hz, 2H), 4.36-4.32 (m, 1H), 4.15-4.00 (m, 2H), 3.90 (dt, *J* = 6.2, 5.7 Hz, 1H), 3.79-3.74 (m, 2H), 3.80 (s, 3H), 3.54-3.46 (m, 1H), 3.43-3.35 (m, 1H), 2.50 (d, *J* =1.3 Hz, 1H), 2.49 (s, 1H), 2.26 (d, *J* = 13.1 Hz, 1H), 2.16 (d, *J* = 13.1 Hz, 1H), 1.94 (q, *J* = 12.7 Hz, 2H), 1.88-1.76 (m, 3H), 1.67-1.60 (m, 3H), 1.22 (t, *J* = 6.7 Hz, 3H), 1.08 (s, 9 H), 0.13 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 177.8, 159.3, 144.9, 135.9, 134.2, 131.4, 129.9, 129.6, 128.0, 114.1, 108.9, 75.2, 75.2, 72.9, 71.9, 66.9, 60.9, 60.6, 55.6, 44.4, 43.1, 42.6, 41.4, 41.2, 38.0, 27.2, 19.5, 14.5, 0.6.



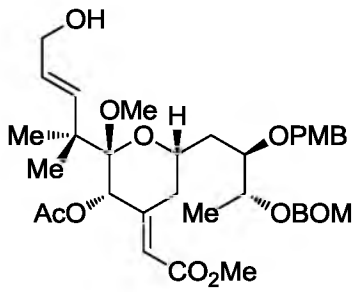
(*S*)-1-((2*R*,6*S*)-6-((*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-((4-methoxybenzyl) oxy)butyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-4-((trimethylsilyl)methyl)pent-4-en-2-ol (2.26).[6] Powdered $CeCl_3$•$7H_2O$ (1.63 g, 4.37 mmol, 10 equiv) in a 25 ml rb flask, was dried at 170 °C under a vacuum of 0.2 mm of Hg for 18 h. The flask was cooled to rt, flushed with Ar, and THF (2 mL) was added. The suspension was stirred for 2 h. Separately, oven dried Mg turnings (110 mg, 4.37 mmol, 10.0 equiv) and a single crystal

of I_2 in a 25 mL round bottom flask, was heated using a heat gun until I_2 sublimed. THF (5 mL) and $TMSCH_2Cl$ (0.61 mL, 4.37 mmol, 10.0 equiv) were added and the mixture was brought to reflux using the heat gun. After 1.5 h, the $TMSCH_2MgCl$ solution was added dropwise to the $CeCl_3$ suspension at -78 °C via cannula. This solution was stirred at -78 °C for 1 h, then ethyl ester **2.x** (327 mg, 0.44 mmol, 1.0 equiv) was added in THF (2.0 mL + 0.5 mL rinse) via cannula. This solution was stirred at -78 °C for 2 h then allowed to reach rt as it stirred overnight. The mixture was transferred to a 125 mL Erlenmeyer flask, diluted with THF (40 mL), and cooled to -78 °C. To this vigorously stirred solution was added a 1 N aqueous HCl solution 5 drops at a time until only a single spot was observed by TLC. The reaction mixture was then transferred into a 250 mL separatory funnel that contained a mixture of a saturated aqueous $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2.0 × 30.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 10 mL fractions. The product containing fractions (15-31) were combined and concentrated under reduced pressure to yield β-hydroxyallylsilane **2.26** (223 mg, 71%) as a clear oil: R_f = 0.61 (20% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.67-7.62 (m, 4H), 7.43-7.38 (m, 6H), 7.18 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.70 (dd, J = 10.7, 1.4 Hz, 2H), 4.64 (d, J = 15.5 Hz, 2H), 4.39 (Aβq, J = = 10.7 Hz, Δν = 28.2 Hz, 2H), 3.98-3.92 (m, 1H), 3.79 (s, 3H), 3.76-3.72 (m, 3H), 3.52-3.46 (m, 3H), 2.26-2.13 (m, 3H), 2.05 (dd, J = 13.6, 6.6 Hz, 1H), 1.99 (dd, J = 12.1, 12.1 Hz, 1H), 1.80-1.78 (m, 2H), 1.72-1.58 (m, 4H), 1.55 (s, 2H), 1.05 (s, 9H), 0.02 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 159.4, 144.8, 144.3, 135.9,

134.2, 134.2, 131.3, 129.9, 129.8, 129.7, 128.0 114.1, 110.2, 109.2, 79.5, 75.7, 73.0, 71.7, 69.8, 60.7, 55.6, 46.8, 42.8, 42.1, 41.4, 41.3, 37.7, 27.3, 27.1, 19.5, -1.0.

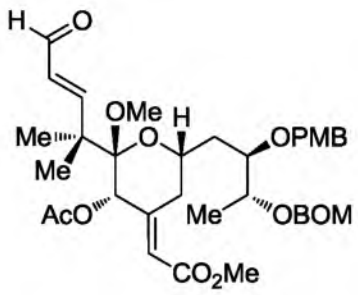
Experimental Procedures and Analytical Data for C-ring **2.34**

The compounds **2.33** and **2.34** were previously prepared by Dr. Yam Poudel and are reported in his Ph.D. thesis and in the literature.[31] These syntheses were repeated on a similar scale to assess these for use in the present work. Compound **2.34** was prepared using an alternative oxidation using activated MnO_2. The experimental procedure and analytical data for these compounds are reproduced here for the convenience of those who may need to repeat this work.



(*E*)-methyl 2-((2*S*,3*S*,6*S*)-3-acetoxy-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((E)-5-hydroxy-2-methylpent -3-en-2-yl)-2-methoxy dihydro-2*H*- pyran-4(3*H*)-ylidene)acetate (2.33).[31] To a stirring solution of the TBS ether **2.32** (620 mg, 0.790 mmol, 1.0 equiv) in THF (15 mL) at 0 °C in a plastic bottle, was added HF•Py (20 % in pyridine, 2.0 mL). TLC analysis after 3 h at 0 °C, indicated complete consumption of the starting material. The mixture was quenched by pipetting into a stirring mixture of saturated aqueous $NaHCO_3$ solution (30 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL).

The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2.0 × 12.0 cm silica gel column, eluting with 30% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (20-36) were combined and concentrated under reduced pressure to yield alcohol **2.33** (480 mg, 91%) as a white foam: R_f = 0.30 (50% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (m, 5H), 7.23-7.18 (m, 2H), 6.86-6.82 (m, 2H), 5.98 (d, *J* = 15.6 Hz, 1H), 5.88 (s, 1H), 5.50 (td, *J* = 15.9, 5.9 Hz, 1H), 5.43 (s, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.68 (s, 2H), 4.61 (d, *J* = 10.7 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.14 (dddd, *J* = 10.7, 6.4, 6.4, 4.4 Hz, 1H), 4.08-4.01 (m, 2H), 3.90 (ddd, *J* = 10.3, 4.4, 2.0 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.45 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.23 (s, 3H), 2.34 (ddd, *J* = 14.2, 10.9, 1.5 Hz, 1H), 2.05 (s, 3H), 1.93 (ddd, *J* = 14.2, 9.8, 2.0 Hz, 1H), 1.73 (ddd, *J* = 13.4, 10.3, 2.4 Hz, 1H), 1.45 (t, *J* = 6.2 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.13 (s, 3H), 1.10 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 169.2, 166.3, 159.0, 152.1, 138.9, 137.7, 130.2, 129.1, 128.2, 126.6, 127.5, 124.6, 117.1, 102.3, 93.1, 76.4, 72.0, 71.8, 71.5, 69.2, 68.2, 63.6, 55.0, 51.2, 51.0, 45.8, 36.0, 32.5, 24.0, 23.6, 21.1, 14.4.

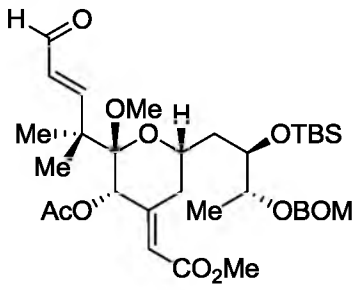


(*E*)-methyl 2-((2*S*,3*S*,6*S*)-3-acetoxy-6-((2*R*,3*R*) -3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-methoxy-2-((*E*)-2-methyl-5-oxopent-3-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-ylidene)acetate (2.34).[31] To a stirring solution of the allylic alcohol **2.33** (480 mg, 0.716 mmol, 1.0 equiv) in benzene (15 mL) at rt in a 25 ml rb flask, was added activated MnO_2 (1.56 g, 17.9 mmol, 25.0 equiv). TLC analysis after 2 h indicated complete consumption of the allylic alcohol starting material. The reaction mixture was filtered over a pad of Celite® and washed with copious amounts of EtOAc. Purification was accomplished by flash column chromatography using a 2.0 × 13.0 cm silica gel column, eluting with 25% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (14-24) were combined and concentrated under reduced pressure to yield aldehyde **2.34** (432 mg, 90%) as a white foam: R_f = 0.39 (40% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.52 (d, *J* = 7.3 Hz, 1H), 7.40-7.28 (m, 5H), 7.22-7.17 (m, 2H), 6.86-6.82 (m, 2H), 5.93 (dd, *J* = 16.1, 7.8 Hz, 1H), 5.89 (s, 1H), 5.39 (s, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.67 (s, 2H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.17 (dddd, *J* = 6.4, 6.4, 6.4, 4.4 Hz, 1H), 4.07 (dddd, *J* = 12.7, 9.8, 2.9, 2.9 Hz, 1H), 3.87 (ddd, *J* = 10.3, 4.4, 2.0 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.53(dd, *J* = 16.1, 2.4 Hz, 1H), 3.26 (s, 3H), 2.36 (ddd, *J* = 14.1, 11.3, 1.4 Hz, 1H), 1.97 (ddd, *J* = 14.1, 11.3, 2.0 Hz, 1H), 1.91 (s, 3H), 1.78 (ddd, *J* = 13.2, 10.3, 2.9 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.16 (s, 3H), 1.14 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.1, 168.4, 166.5, 165.9, 159.0,

151.1, 137.7, 130.1, 129.1, 128.2, 127.5, 127.4, 126.6, 117.6, 113.6, 102.2, 93.1, 76.2, 71.7, 71.2, 71.1, 69.2, 68.9, 55.0, 51.1, 51.0, 47.1, 35.8, 32.4, 23.6, 21.4, 20.9, 14.2.

Experimental Procedures and Analytical Data for Macrolactone **2.24**

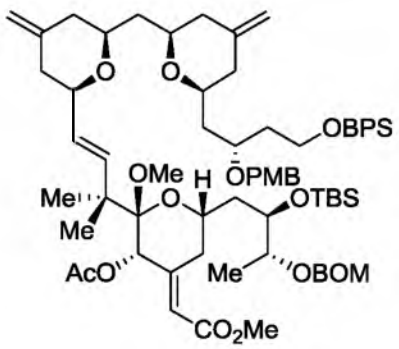
The compounds **2.25**, **2.35**, **2.36**, **2.37**, and **2.24** were previously prepared by Dr. Mark Petersen and are reported in his Ph.D. thesis.[16] These syntheses were repeated on a larger scale to assess these for use in the present work. The experimental procedure and analytical data for these compounds are reproduced here for the convenience of those who may need to repeat this work.



(*E*)-methyl 2-((2*S*,3*S*,6*S*)-3-acetoxy-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)butyl)-2-methoxy-2-((*E*)-2-methyl-5-oxopent-3-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-ylidene)acetate (2.25).[16] To a stirring solution of PMB ether **2.34** (240 mg, 0.359 mmol, 1.0 equiv) and H_2O (70 μL) in CH_2Cl_2 (7 mL) at 0 °C in a 25 ml rb flask, was added DDQ (122 mg, 0.538 mmol, 1.5 equiv). TLC analysis after 2 h at 0 °C indicated complete consumption of the PMB ether starting material. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined

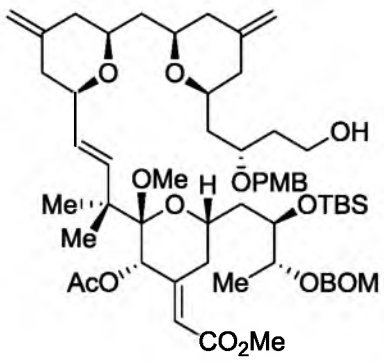
organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the impure alcohol.

To a stirring solution of the crude alcohol and 2,6-lutidine (250 μL, 2.15 mmol, 6.0 equiv) in CH_2Cl_2 (7 mL) in a 25 ml rb flask at 0 °C, was added TBSOTf (190 μL, 1.08 mmol, 3.0 equiv). TLC analysis after 1 h at 0 °C indicated complete consumption of the alcohol starting material. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography using a 2.0 × 15.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 10 × 75 mm test tube fractions. The product containing fractions (33-55) were combined and concentrated under reduced pressure to provide TBS ether **2.25** (190 mg, 80% over 2 steps) as a clear oil: R_f = 0.68 (50% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.53 (d, *J* = 7.8 Hz, 1H), 7.38-7.27 (m, 4H), 5.94 (dd, *J* = 16.1, 4.8 Hz, 1H), 5.91 (s, 1H), 5.50 (s, 1H), 4.80 (ABq, *J* = 7.1 Hz, Δν = 11.9 Hz, 2H), 4.64 (s, 2H), 4.14-4.07 (m, 2H), 3.85 (dt, *J* = 10.9, 6.2 Hz, 2H), 3.70 (s, 3H), 3.53 (dd, *J* = 16.1, 2.5 Hz, 1H), 3.40 (s, 3H), 2.35 (ddd, *J* = 15.1, 11.5, 1.2 Hz, 1H), 2.03 (ddd, *J* = 14.1, 8.8, 2.2 Hz, 1H), 1.93 (s, 3H), 1.65 (ddd, *J* = 14.0, 8.5, 2.8 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.9, 169.1, 167.2, 166.4, 151.6, 137.7, 128.7, 128.0, 127.1, 118.2, 102.5, 93.3, 75.1, 71.0, 70.3, 69.5, 69.1, 52.0, 51.5, 47.5, 38.7, 33.0, 26.1, 26.0, 23.9, 21.9, 21.4, 18.4, 13.9, -3.8, -4.5.



(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy) methoxy)-2-((*tert*-butyldimethylsilyl) oxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*R*,6*S*)-6-((*S*)-4-hydroxy-2-((4-methoxybenzyl)oxy) butyl)-4-methylenetetrahydro-2*H*-pyran-2-yl) methyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene) tetrahydro-2*H*-pyran-3-yl octanoate (2.35).[16] To a stirring solution of aldehyde **2.25** (148 mg, 0.222 mmol, 1.0 equiv) and silane **2.26** (174 mg, 0.224 mmol, 1.1 equiv) in Et_2O (5 mL) in a 15 ml rb flask at -78 °C, was added TMSOTf (1.1 M in Et_2O, 220 μL, 0.244 mmol, 1.1 equiv) via syringe. The reaction was allowed to proceed for 6 h at -78 °C, after which time TLC analysis indicated complete consumption of the aldehyde starting material. The reaction mixture was quenched by transfer into a 25 mL separatory funnel that contained a mixture of a saturated aqueous $NaHCO_3$ solution (5 mL) and Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography using a 2.0 × 18.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 10 mL fractions. The product containing fractions (6-24) were concentrated to give bispyran **2.35** (210 mg, 73%) as a white foam. R_f = 0.46 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.73-7.65 (m, 4H), 7.47-7.24 (m, 11H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 5.96 (d, *J* = 16.1 Hz, 2H), 5.90 (s, 1H),

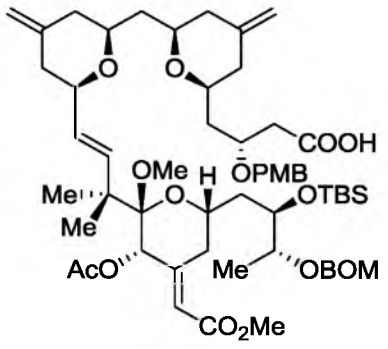
5.56 (s, 1H), 5.41 (dd, J = 16.0, 5.6 Hz, 1H), 4.80 (s, 1H), 4.72 (d, J = 11.0 Hz, 2H), 4.64 (s, 2H), 4.64 (s, 1H), 4.54 (s, 1H), 4.42 (ABq, J = 10.3 Hz, $\Delta\nu$ = 35.7 Hz, 2H), 4.14-4.04 (m, 2H), 3.96-3.90 (m, 1H), 3.89-3.68 (m, 2H), 3.79 (s, 3H), 3.77-3.71 (m, 2H), 3.69 (s, 3H), 3.60-3.42 (m, 5H), 3.31 (s, 3H), 2.42-2.12 (m, 4H), 2.08 (s, 3H), 2.04-1.84 (m, 6H), 1.82-1.73 (m, 2H), 1.69-1.55 (m, 3H), 1.18 (d, J = 6.4 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.06 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 169.5, 166.7, 159.3, 153.0, 145.0, 144.3, 138.3, 135.8, 134.1, 131.1, 129.8, 129.6, 128.5, 128.0, 127.9, 127.8, 127.0, 117.0, 114.0, 109.0, 108.7, 102.6, 93.2, 79.1, 77.4, 75.0, 75.0, 74.9, 72.8, 72.2, 71.7, 70.2, 69.6, 68.4, 60.5, 55.5, 51.6, 51.4, 46.1, 43.0, 42.5, 41.4, 41.1, 40.9, 40.4, 38.7, 38.0, 33.5, 27.2, 27.1, 27.0, 26.2, 24.3, 24.0, 21.5, 19.4, 18.3, 14.0, -3.8, -4.4.



(*E*)-methyl 2-((2*S*,3*S*,6*S*)-3-acetoxy-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)butyl)-2-((*E*)-4-((2 *R*,6*S*)-6-(((2*R*,6*S*)-6-((*S*)-4-hydroxy-2-((4-methoxybenzyl)oxy)butyl)-4-methylene tetrahydro-2*H*-pyran-2-yl)methyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-methyl but-3-en-2-yl)-2-methoxydihydro-2*H*-pyran-4(3*H*)-ylidene)acetate (2.36).[16] A stock solution of 0.5 M TBAF/ AcOH was prepared by adding TBAF (1M in THF, 0.5 mL) to a stirring solution of AcOH (1M in DMF, 0.5 mL) in a 1 mL volumetric flask and stirred at rt for 10 min.

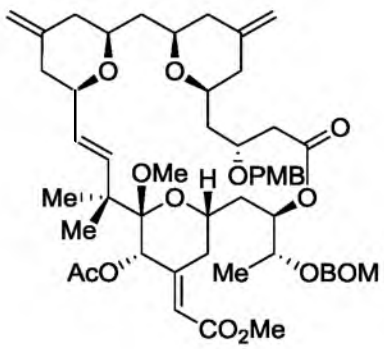
To a stirring solution of BPS ether **2.35** (92 mg, 0.067 mmol, 1.0 equiv) and DMF (3.0 mL) in a 10 ml rb flask at 0 °C, was added TBAF (0.5 M buffered with 100 mol% AcOH in DMF/THF, 264 μL, 0.132 mmol, 1.0 equiv) via volume pipette. The reaction was allowed to proceed for 19 h at rt, after which time TLC analysis indicated complete consumption of the BPS ether starting material. The reaction mixture was quenched by transfer into a 25 mL separatory funnel that contained a mixture of a H_2O (10 mL) and 25% EtOAc/hexanes (10 mL). The layers were separated and the aqueous layer was extracted with 25% EtOAc/hexanes (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2.0 × 16.0 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 10 mL fractions. The product containing fractions (30-79) were combined and concentrated under reduced pressure to yield alcohol **2.36** (104 mg, 75%) as a clear oil: R_f = 0.46 (50% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.22 (m, 7H), 6.89 (d, J = 8.4 Hz, 2H), 5.97 (d, J = 16.4 Hz, 1H), 5.90 (s, 1H), 5.54 (s, 1H), 5.41 (dd, J = 15.8, 6.2 Hz, 1H), 4.80 (s, 2H), 4.73 (s, 2H), 4.66 (s, 1H), 4.64 (s, 2H), 4.58 (s, 1H), 4.48 (ABq, J = 10.4 Hz, Δν = 24.5 Hz, 2H), 4.13-4.04 (m, 2H), 3.93-3.82 (m, 2H), 3.80 (s, 3H), 3.76-3.70 (m, 2H), 3.69 (s, 3H), 3.56-3.40 (m, 4H), 3.32 (s, 3H), 2.47-2.32 (m, 2H), 2.28-2.15 (m, 4H), 2.09 (s, 3H), 2.06-1.87 (m, 8H), 1.84-1.53 (m, 6H), 1.17 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.09 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 169.6, 166.7, 159.5, 153.0, 144.6, 144.3, 138.6, 138.1, 130.6, 129.7, 128.6, 128.0, 128.0, 127.9, 126.9, 117.0, 114.1, 109.1, 109.0, 102.6, 93.2, 79.4, 77.4, 75.4, 75.3, 75.0, 75.0, 74.9, 72.1, 71.6, 70.1, 69.5, 68.4, 60.4, 55.5, 51.6,

51.4, 46.2, 42.9, 41.8, 41.4, 41.0, 40.9, 40.5, 38.6, 36.8, 33.4, 26.1, 24.2, 23.9, 21.5, 18.3, 13.9, -3.8, -4.5.



(*R*)-4-((2*S*,6*R*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-3-acetoxy-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethyl silyl)oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2*H*-pyran-2-yl)-3-methylbut-1-en-1-yl)-4-methylenetetrahydro-2*H*-pyran-2-yl)methyl)-4-methyl enetetrahydro-2*H*-pyran-2-yl)-3-((4-methoxybenzyl)oxy)butanoic acid (2.37).[16] To a stirring solution of alcohol **2.26** (100 mg, 0.095 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) in a 10 ml rb flask at -5° C, was added (iPr)$_2$NEt (116 μL, 0.665 mmol, 7.0 equiv) and DMSO (68 μL, 0.950 mmol, 10.0 equiv). Stirring continued for 10 min at -5° C, and then SO_3•Py (45 mg, 0.286 mmol, 3.0 equiv) was added. The reaction was allowed to proceed for 1 h at -5° C, after which time TLC analysis indicated complete consumption of the alcohol starting material. The solution was quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol was used in the next step without purification.

To a stirring solution of crude aldehyde in 2-methyl-2-butene (1.4 mL) and *t*BuOH (1.4 mL) in a 10 ml rb flask at -15° C, was added aqueous KH_2PO_4 solution (1.25 M, 0.5 mL) followed by $NaClO_2$ (80%, 107 mg, 0.950 mmol, 10.0 equiv). The reaction was allowed to proceed for 4 h at -15° C. The solution was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL) and diluted with EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2.0 × 20.0 cm silica gel column, eluting with 3% MeOH/CH_2Cl_2, collecting 10 mL fractions. The product containing fractions (7-17) were combined and concentrated under reduced pressure to yield acid **2.37** (88 mg, 90%) as an oil: R_f = 0.30 (10% MeOH/CH_2Cl_2); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.44-7.20 (m, 7H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.99 (d, *J* = 16.0 Hz, 1H), 5.90 (s, 1H), 5.55 (s, 1H), 5.42 (dd, *J* = 15.8, 6.1 Hz, 1H), 4.81 (s, 2H), 4.73 (s, 2H), 4.65 (s, 2H), 4.59 (s, 1H), 4.51 (ABq, *J* = 11.1 Hz, Δν = 57.6 Hz, 2H), 4.15-4.03 (m, 2H), 3.89-3.83 (m, 1H), 3.80 (s, 3H), 3.76-3.70 (m, 1H), 3.69 (s, 3H), 3.57-3.39 (m, 4H), 3.31 (s, 3H), 2.62 (d, *J* = 5.9, 5.9 Hz, 1H), 2.42-2.31 (m, 1H), 2.29-2.12 (m, 5H), 2.09 (s, 3H), 2.06-1.84 (m, 8H), 1.82-1.49 (m, 4H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 174.5, 169.7, 166.7, 159.5, 153.0, 144.4, 144.3, 138.8, 137.9, 130.2, 129.7, 128.6, 128.1, 128.0, 127.9, 126.9, 117.0, 114.1, 109.1, 102.6, 93.1, 79.5, 77.4, 75.1, 75.0, 74.9, 75.0, 73.1, 72.4, 71.7, 70.1, 69.5, 68.4, 55.5, 51.6, 51.4, 46.1, 42.9, 42.0, 41.2, 40.9, 40.8, 40.5, 40.2, 38.6, 33.5, 26.1, 24.3, 23.8, 21.5, 18.3, 13.9, -3.8, -4.5.



(*E*)-methyl 2-((1*R*,3*S*,7*R*,11*S*,12*S*,15*S*, 17*R*,21*R*,23*S*,*E*)-12-acetoxy-17-((*R*)-1-((benzyloxy)methoxy)ethyl)-11-methoxy-21-((4-methoxybenzyl)oxy)-10,10-dimethyl-5,25-dimethylene-19-oxo-18,27,28,29-tetra oxatetracyclo[21.3.1.1^{3,7}.1^{11,15}]nonacos-8-en-13-ylidene)acetate (2.24).[16] To a stirring solution of the TBS ether **2.37** (65 mg, 0.0611 mmol, 1.0 equiv) in THF (3 mL) at 0 ºC in a 14 mL plastic bottle, was added HF•py (20 % in pyridine, 1.5 mL). TLC analysis after 74 h at rt indicated complete consumption of the TBS ether starting material. The mixture was quenched by pipetting into a stirring mixture of saturated aqueous $NaHCO_3$ solution (25 mL) and Et_2O (25 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was taken onto the next step without further purification

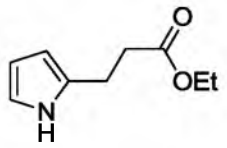
To a stirring solution of the seco acid in THF (3 mL) in a 10 ml rb flask at 0 °C, were added Et_3N (51 µL, 0.367 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (29 µL, 0.183 mmol, 3.0 equiv) via syringe. After 10 min, the reaction mixture was warmed to rt and stirring was continued for an additional 3 h. The reaction mixture was then diluted with toluene (20 mL) and taken up into a 25 mL gas-tight syringe. This solution was added by syringe pump to a stirring solution of DMAP (52 mg, 0.444 mmol, 20.0 equiv) in toluene (40 mL) in a 250 ml rb flask at 40 °C, over 16 h. The residual contents of the syringe were

rinsed into the flask with toluene (2 × 2 mL) and stirring was continued for an additional 2 h. The reaction mixture was cooled to rt, washed with saturated aqueous $NaHCO_3$ solution (25 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2.0 × 15.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 10 mL fractions. The product containing fractions (53-83) were combined and concentrated under reduced pressure to yield macrolactone **2.24** (40 mg, 70%) as a white foam: R_f = 0.39 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.42-7.28 (m, 5H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 6.23 (d, *J* = 15.8 Hz, 1H), 5.95 (s, 1H), 5.62-5.53 (m, 1H), 5.34 (dd, *J* = 15.6, 8.5 Hz, 1H), 5.16 (s, 1H), 4.82 (ABq, *J* = 6.9 Hz, Δν = 14.1 Hz, 2H), 4.76 (s, 2H), 4.71 (s, 2H), 4.64 (ABq, *J* = 11.9 Hz, Δν = 24.7 Hz, 2H), 4.48 (s, 2H), 4.22-4.14 (m, 1H), 4.00-3.92 (m, 2H), 3.74 (s, 3H), 3.73-3.70 (m, 2H), 3.69 (s, 3H), 3.55-3.47 (m, 1H), 3.41-3.32 (m, 1H), 3.09 (s, 3H), 2.58 (dd, *J* = 15.2, 1.5 Hz, 1H), 2.47 (dd, *J* = 15.6, 10.4 Hz, 2H), 2.31 (d, *J* = 13.0 Hz, 1H), 2.22-2.08 (m, 4H), 2.05 (s, 3H), 2.03-1.82 (m, 5H), 1.79-1.66 (m, 2H), 1.56 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.50-1.39 (m, 2H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.2, 169.3, 166.9, 159.3, 151.4, 144.5, 144.4, 141.8, 138.1, 130.9, 129.6, 128.6, 127.1, 127.8, 125.6, 119.5, 113.9, 109.1, 109.0, 103.3, 93.7, 81.5, 76.5, 76.4, 76.3, 75.3, 73.9, 73.1, 72.1, 70.7, 69.8, 67.3, 55.5, 52.8, 51.4, 45.2, 44.2, 43.1, 41.9, 41.5, 41.1, 40.9, 41.1, 34.6, 30.9, 29.9, 26.3, 21.6, 20.2, 15.2.

Experimental Procedures and Analytical Data for BODIPY FL

Tag **2.34** and **2.47**

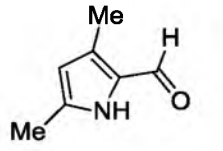
The compounds **2.39**, **2.40**, **2.41**, and **2.34** were previously prepared and are reported in the literature.[19] The synthesis of the BODIPY FL acid **2.34** was repeated on half the scale to assess these for use in the present work. The compounds **2.48** and **2.47** were also previously prepared and are reported in the literature.[21] The synthesis of the BODIPY FL azide **2.47** was repeated on a similar scale to assess these for use in the present work. The experimental procedure and analytical data for BODIPY FL acid **2.34** and BODIPY FL azide **2.47** are reproduced here for the convenience of those who may need to repeat this work.



Ethyl 3-(1*H*-pyrrol-2-yl)propanoate (2.39).[19] To a stirring solution of 1*H*-pyrrole-2-carbaldehyde (5.20 g, 54.7 mmol, 1.0 equiv) in toluene (60 mL) in a 250 mL round bottom flask, was added ethyl 3-(triphenylphosphoranylidene)propanoate (21.0 g, 60.2 mmol, 1.1 equiv). The reaction mixture was heated at 50 °C for 14 h, and then allowed to cool to rt. The mixture was filtered over a silica (3 × 9 cm) pad and washed with copious amounts of 50% EtOAc/hexanes. The filtrate was concentrated under reduced pressure to give the crude product as an orange oil. This material was carried onto the next step without further purification.

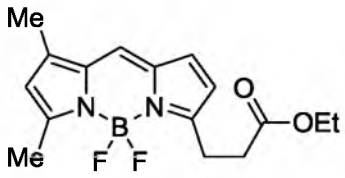
A 250 mL Parr bomb was charged with a magnetic stir bar, the crude olefin, palladium (10% on carbon, 10 g), and ethanol (50 mL). The gas inlet tube was attached to a hydrogen

source and hydrogen was introduced into the reaction vessel until the pressure gauge indicated 500 psi. The pressure was carefully released to 1 atm by opening the stop valve. This procedure was repeated 2 times, and finally hydrogen was pressurized to 500 psi. The reaction solution was stirred at rt for 26 h, during which time the hydrogen cylinder was kept connected. After the main valve of the hydrogen cylinder was closed, excess hydrogen in the reaction tube was carefully bled off, and the apparatus was disassembled. The reaction mixture was filtered through a Celite pad (3 × 8 cm), washed with copious amounts of 50% EtOAc/hexanes, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography on a 12 × 14 cm column, eluting with 10% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (10–24) were combined and concentrated under reduced pressure to give ester **2.39** (7.0 g, 78% yield) as a pale yellow oil: R_f = 0.65 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 8.59 (brs, 1H), 6.69 (d, *J* = 1.0 Hz, 1H), 6.13 (dd, *J* = 2.9, 2.4 Hz, 1H), 6.69 (d, *J* = 1.0 Hz, 1H), 4.19 (q, *J* = 7.3 Hz, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.66 (t, *J* = 7.3 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 174.3, 131.2, 116.9, 108.1, 105.6, 60.9, 34.7, 32.7, 14.3.



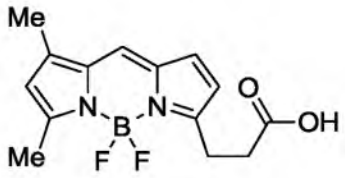
3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (2.40).[19] To a stirring solution of commercially available 2,4-dimethyl-1*H*-pyrrole (4.3 g, 45.2 mmol, 1.0 equiv) and DMF (30 mL) in a 100 mL round bottom flask at 0 °C, was added $POCl_3$ (4.6 mL, 49.7 mmol, 1.1 equiv) over 20 min via syringe. The reaction was allowed to proceed for 2 h at rt, after which time TLC analysis indicated complete consumption of the pyrrole starting material.

The iminium salt was then quenched by pouring the reaction mixture into a stirring solution of aqueous NaOH solution (300 mL of 6M) and stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by filtration over a plug of alumina (5 × 15 cm). The plug was flushed with copious amounts of 30% EtOAc/hexanes. The filtrate was concentrated under reduced pressure to give pure product **2.40** (4.5 g, 80% yield) as a yellow solid: mp 80–81 °C; R_f = 0.35 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 10.44 (brs, 1H), 9.47 (s, 1H), 5.86 (s, 1H), 2.33 (s, 3H), 2.32 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 176.1, 139.0, 135.1, 128.9, 13.3, 10.8.



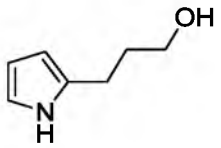
3-(3-ethoxy-3-oxopropyl)-5,5-difluoro-7,9-di methyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (2.41).[19] To a stirring solution of pyrrole **2.39** (603 mg, 3.61 mmol, 1.0 equiv) and CH_2Cl_2 (30 mL) in a 100 mL round bottom flask at 0 °C, was added aldehyde **2.40** (489 mg, 3.97 mmol, 1.1 equiv) followed by $POCl_3$ (0.34 mL, 3.97 mmol, 1.1 equiv) via syringe. The reaction was allowed to proceed for 2 h at rt, after which time TLC analysis indicated complete consumption of the pyrrole **2.39** starting material. The solution was cooled to 0 °C, and (iPr)$_2$NEt (3.5 mL, 19.9 mmol, 5.0 equiv) and BF_3•OEt_2 (2.0 mL, 15.9 mmol, 4.0 equiv) were added dropwise via syringe. The solution was stirred for 16 h during which it slowly returned to rt. The solution was diluted with H_2O (50 mL), the phases were separated, and the aqueous phase was extracted with

CH_2Cl_2 (2 × 50 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography on a 5 × 15 cm column, eluting with 20% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (16–31) were combined and concentrated under reduced pressure to give **2.41** (720 mg, 62% yield) as a red solid: mp 76–77 °C; R_f = 0.34 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 1H), 6.88 (d, J = 3.9 Hz, 1H), 6.27 (d, J = 3.9 Hz, 1H), 6.12 (s, 1H), 4.16 (q, J = 7.3 Hz, 2H), 3.30 (t, J = 7.3 Hz, 2H), 2.76 (t, J = 7.3 Hz, 2H), 2.57 (s, 3H), 2.24 (s, 3H), 1.26 (t, J = 7.3 Hz, 2H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.7, 160.5, 157.5, 144.0, 135.4, 133.5, 128.3, 124.0, 120.6, 116.9, 60.7, 33.6, 24.2, 15.1, 14.4, 11.5.

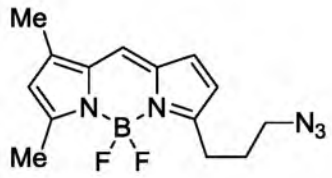


3-(2-carboxyethyl)-5,5-difluoro-7,9-dimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-4-ium-5-uide (2.42).[19] To a stirring solution of ester **2.41** (610 mg, 1.91 mmol, 1.0 equiv) and THF/H_2O (3:2, 150 mL) in a 500 mL round bottom flask at rt, was added HCl (37% in H_2O, 40 mL) via pipet. The reaction was allowed to proceed for 26 h at rt, after which time TLC analysis indicated complete consumption of the ester starting material. The solution was diluted with CH_2Cl_2 (100 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography on a 5 × 12 cm column, eluting with 1%

MeOH/ CH_2Cl_2, collecting 8 mL fractions. The product containing fractions (12–18) were combined and concentrated under reduced pressure to give **2.42** (360 mg, 65% yield) as a red solid: mp 179–181 °C; R_f = 0.40 (10% MeOH/ CH_2Cl_2); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.07 (brs, 1H), 7.38 (s, 1H), 7.01 (d, *J* = 3.9 Hz, 1H), 6.33 (d, *J* = 3.9 Hz, 1H), 6.23 (s, 1H), 3.15 (t, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.51 (s, 3H), 2.26 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 174.0, 161.6, 157.8, 146.1, 136.2, 134.2, 129.4, 125.9, 121.6, 117.3, 32.9, 24.6, 15.1, 11.4.



3-(1*H*-pyrrol-2-yl)propan-1-ol (2.48).[21] To a stirring solution of ester **2.39** (3.17 g, 19.0 mmol, 1.00 equiv) in ether (150 mL) in a 500 ml rb flask at 0° C, was added lithium aluminum hydride (1.08 g, 28.4 mmol, 1.5 equiv) in 3 portions over 10 mins. The reaction was allowed to proceed for 4 h at rt, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of H_2O (1.1 mL), aqueous NaOH solution (1.1 mL of 15%), and then with an additional amount of H_2O (3.3 mL). Stirring was continued for 1 h at rt. The solution was dried over $MgSO_4$, stirred for 15 min, filtered, and concentrated under reduced pressure to give alcohol **2.48** (2.38 g, 100% yield) as a clear yellow oil: R_f = 0.17 (50% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 8.37 (brs, 1H), 6.70-6.68 (m, 1H), 6.17-6.14 (m, 1H), 5.98-5.94 (m, 1H), 3.71 (t, *J* = 5.9 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.10 (brs, 1H), 1.89 (tt, *J* = 6.8, 6.8 Hz, 2H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 132.0, 116.6, 108.3, 105.2, 62.4, 32.4, 24.3.



3-(3-azidopropyl)-5,5-difluoro-7,9-dimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-4-ium-5-uide (2.47).[21] To a stirring solution of alcohol **2.48** (2.38 g, 19.0 mmol, 1.0 equiv) and Et_3N (5.3 mL, 38.0 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL) in a 100 ml rb flask at 0 °C, was added methanesulfonyl chloride (1.2 mL, 12.1 mmol, 1.0 equiv) via syringe. The reaction was allowed to proceed for 4h at rt, after which time TLC analysis indicated complete consumption of the alcohol starting material. The reaction mixture was quenched by transfer into a 100 mL separatory funnel that contained a mixture of a saturated aqueous $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. This material was carried onto the next step without further purification.

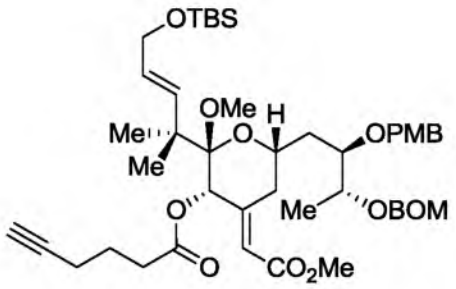
To a stirring solution of the crude mesylate in DMF (50 mL) in a 100 ml rb flask, was added sodium azide (3.7 g, 57.0 mmol, 3.0 equiv). The reaction was allowed to proceed for 16 h at 70 °C, and then allowed to cool to rt. The solution was diluted with H_2O (25 mL) and 30% EtOAc/hexanes (25 mL), the phases were separated, and the aqueous phase was extracted with 30% EtOAc/hexanes (2 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. This material was carried onto the next step without further purification.

To a stirring solution of crude pyrrole and CH_2Cl_2 (200 mL) in a 500 mL round bottom flask at 0 °C, was added 3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (2.3 g, 19.0

mmol, 1.0 equiv) followed by $POCl_3$ (2.0 mL, 20.9 mmol, 1.1 equiv) via syringe. The reaction was allowed to proceed for 2 h at rt. The solution was cooled to 0 °C, and $(i\text{Pr})_2\text{NEt}$ (16.5 mL, 95.0 mmol, 5.0 equiv) followed by $BF_3\bullet OEt_2$ (11.7 mL, 95.0 mmol, 5.0 equiv) were added dropwise via syringe. The solution was stirred for 18 h during which it slowly returned to rt. The reaction mixture was quenched slowly with H_2O (100 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography on a 4 × 35 cm column, eluting with 5% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (22–44) were combined and concentrated under reduced pressure to give **2.47** (3.17 g, 55% yield, 3 steps) as a red solid: mp 49–50 °C; R_f = 0.35 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H), 6.91 (d, J = 3.9 Hz, 1H), 6.28 (d, J = 4.0 Hz, 1H), 6.12 (s, 1H), 3.39 (t, J = 6.9 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.57 (s, 3H), 2.25 (s, 3H), 2.04 (tt, J = 7.9, 7.9 Hz, 2H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 160.4, 157.9, 143.9, 135.3, 133.4, 128.3, 123.9, 120.6, 116.8, 51.1, 28.3, 26.0, 15.1, 11.5.

Experimental Procedures and Analytical Data for C-ring **2.50**

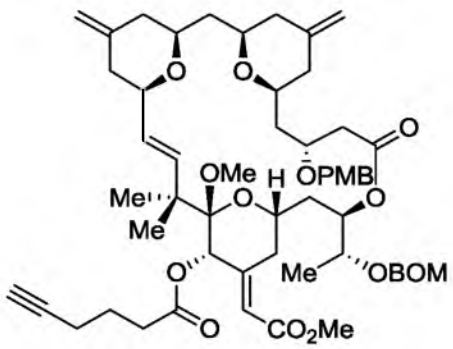
and Merle 44



(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyl oxy)methoxy)-2-((4-methoxybenzyl)oxy) butyl)-2-((*E*)-5-((*tert*-butyldimethylsilyl)oxy) -2-methylpent-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2*H*-pyran-3-yl hex-5-ynoate (2.50). To a stirring solution of acetate **2.32** (135 mg, 0.172 mmol, 1.0 equiv) in MeOH (10 mL) in a 25 mL round bottom flask at rt, was added K_2CO_3 (237 mg, 1.72 mmol, 10.0 equiv). The reaction was allowed to proceed for 1 h, after which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by transfer into a 100 mL separatory funnel that contained a mixture of saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated to give the crude alcohol that was taken directly onto the next reaction without further purification.

To a stirring solution of 5-hexynoic acid (36 μL, 0.344 mmol, 2.0 equiv), Et_3N (140 μL, 1.03 mmol, 6.0 equiv), and toluene (7 mL) in a 15 mL round bottom flask at rt, was added 2,4,6-trichlorobenzoyl chloride (54 μL, 0.344 mmol, 2.0 equiv) via syringe. The reaction was allowed to proceed for 5 h at rt, after which time the solution was added to the neat crude alcohol in a 15 mL round bottom flask via cannula, followed by the addition

of DMAP (210 mg, 1.72 mmol, 10.0 equiv). The reaction was allowed to proceed for 1 h at rt. Purification was accomplished by directly loading the suspension onto a 2 × 17 cm silica gel flash column, rinsing with toluene, then eluting with 10% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (20-41) were combined and concentrated under reduced pressure to yield alkyne **2.50** (118 mg, 82%) as a white foam: R_f = 0.51 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -3.7 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.43-7.19 (m, 7H), 6.89-6.81 (m, 2H), 6.00 (d, *J* = 15.9 Hz, 1H), 5.89 (s, 1H), 5.41 (s, 1H), 5.38 (ddd, *J* = 9.6, 4.5, 4.5 Hz, 1H), 4.86 (d, *J* = 3.0 Hz, 2H), 4.66 (s, 2H), 4.63 (d, *J* = 12.6 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.17-4.10 (m, 3H), 4.05 (dddd, *J* = 12.0, 10.1, 2.3, 2.3 Hz, 1H), 3.90 (ddd, *J* = 9.6, 4.2, 1.3 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.53 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.24 (s, 3H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.33-2.22 (m, 2H), 1.98 (dd, *J* = 2.6, 2.6 Hz, 1H), 1.92 (ddd, *J* = 14.5, 10.2, 1.6 Hz, 1H), 1.87-1.78 (m, 2H), 1.74 (ddd, *J* = 13.0, 10.2, 2.1 Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.12 (s, 6H), 0.91 (s, 9H), 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.5, 166.6, 159.3, 152.4, 138.0, 138.1, 130.7, 129.8, 129.4, 128.6, 128.0, 127.9, 117.7, 114.0, 102.8, 93.5, 83.2, 76.9, 72.5, 72.2, 72.1, 69.6, 69.6, 68.5, 55.4, 51.7, 51.3, 45.9, 36.4, 33.1, 32.6, 26.2, 24.6, 23.6, 23.4, 18.6, 17.9, -4.9; DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 51.7, 51.3, 26.2, 24.6, 23.6, -4.9; CH_2 δ 93.5, 72.1, 69.6, 64.6, 36.4, 33.1, 32.6, 23.4, 17.9; CH δ 138.1, 129.8, 129.4, 128.6, 128.0, 127.9, 117.7, 114.0, 76.9, 72.5, 72.2, 69.6, 68.5; CH_0 δ 171.5, 166.6, 159.3, 152.4, 138.0, 130.7, 102.8, 83.2, 45.9, 18.6; IR (neat) 3304, 2952, 2856, 1742, 1720, 1612, 1513, 1462, 1432, 1383, 1249, 1152, 1106, 1040, 836, 777 cm^{-1}; HRMS (ESI) calcd for $C_{47}H_{68}NaO_{11}Si$ (M+Na) 859.4429, found 859.4432.

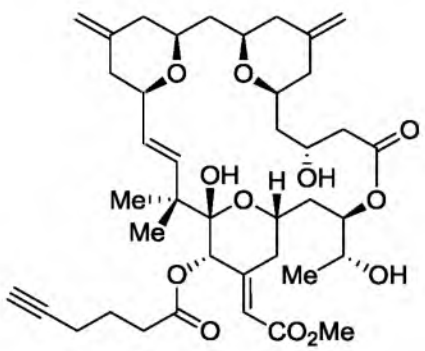


(1*R*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*, 21*R*,23*S*) -17-((*R*)-1- ((benzyloxy) methoxy)ethyl) -11-methoxy -13-(2-methoxy-2-oxo ethylidene) -21-((4-methoxybenzyl)oxy) -10,10 –dimethyl -5,25-dimethylene -19-oxo-18,27,28,29 – tetraoxatetracyclo [21.3.1.1^{3,7}.1^{11,15}] nonacos-8-en-12-yl hex-5-ynoate (2.52): To a stirring solution of acetate **2.24** (8.9 mg, 0.0096 mmol, 1.0 equiv) in MeOH (2 mL) in a 4 mL vial at rt, was added K_2CO_3 (13 mg, 0. 096 mmol, 10.0 equiv). The reaction was allowed to proceed for 45 min at rt, after which time TLC analysis indicated complete consumption of the ester starting material. The reaction mixture was transferred into a 25 mL separatory funnel that contained a mixture of CH_2Cl_2 (5 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude alcohol was used without further purification.

To a stirring solution of 5-hexynoic acid (6 μL, 0.055 mmol, 5.0 equiv), Et_3N (15 μL, 0.110 mmol, 10.0 equiv), and toluene (1 mL) in a 4 mL vial at 0 °C, was added 2,4,6-trichlorobenzoyl chloride (9 μL, 0.055 mmol, 5.0 equiv) via syringe. The reaction was allowed to proceed for 3 h at rt, after which time the solution was added to the neat crude alcohol in a 4 mL vial via cannula, followed by the addition of DMAP (13 mg, 0.110 mmol, 10.0 equiv). The reaction was allowed to proceed for 1 h at rt, after which time TLC

analysis indicated complete consumption of the alcohol starting material. Purification was accomplished by directly loading the suspension onto a 1.0 × 7.0 cm silica gel flash column, rinsing with toluene, then eluting with 30% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (7-22) were combined and concentrated under reduced pressure to yield ester **2.52** (7.6 mg, 70%) as a clear film: R_f = 0.39 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +29 (c = 0.3, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.41-7.28 (m, 5H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.23 (d, *J* = 15.5 Hz, 1H), 5.95 (s, 1H), 5.60-5.55 (m, 1H), 5.34 (dd, *J* = 15.8, 8.8 Hz, 1H), 5.18 (s, 1H), 4.82 (ABq, *J* = 7.0 Hz, Δν = 14.5 Hz, 2H), 4.76 (s, 2H), 4.71 (s, 2H), 4.64 (ABq, *J* = 11.9 Hz, Δν = 24.2 Hz, 2H), 4.48 (s, 2H), 4.22-4.15 (m, 1H), 4.00-3.92 (m, 2H), 3.75 (s, 3H), 3.73-3.71 (m, 2H), 3.69 (s, 3H), 3.54-3.45 (m, 1H), 3.41-3.33 (m, 1H), 3.27-3.19 (m, 1H), 3.09 (s, 3H), 2.58 (dd, *J* = 15.0, 2.6 Hz, 1H), 2.51-2.42 (m, 2H), 2.32 (d, *J* = 12.4 Hz, 2H), 2.24 (td, *J* = 7.8, 2.6 Hz, 2H), 2.18 (t, *J* = 8.9 Hz, 2H), 2.15-2.02 (m, 2H), 2.00-1.92 (m, 4H), 1.91-1.79 (m, 4H), 1.77-1.59 (m, 2H), 1.56 (dd, *J* = 15.0, 7.8 Hz, 1H), 1.50-1.41 (m, 1H), 1.30-1.15 (m, 4H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.92-0.83 (m, 1H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.3, 171.5, 167.0, 159.3, 151.3, 144.5, 144.4, 141.8, 138.1, 130.9, 129.6, 128.6, 128.1, 127.8, 125.7, 119.5, 113.9, 109.1, 109.0, 103.3, 93.7, 83.1, 81.5, 81.5, 77.4, 76.4, 75.3, 73.9, 73.2, 72.1, 70.7, 69.8, 69.5, 67.2, 55.4, 52.8, 51.4, 45.2, 44.2, 43.1, 41.9, 41.4, 41.1, 41.0, 40.9, 34.7, 33.3, 31.0, 29.9, 26.5, 23.3, 20.2, 17.9, 15.2, 14.3; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 54.4, 52.8, 26.5, 20.2, 15.2; CH_2 δ 109.1, 109.0, 93.7, 72.1, 69.8, 44.2, 43.1, 41.9, 41.9, 41.4, 41.1, 41.0, 40.9, 34.7, 33.3, 31.0, 29.9, 23.4, 17.9, 14.3; CH δ 141.8, 129.6, 128.1, 127.8, 125.7, 119.6, 113.9, 83.1, 81.5, 77.4, 76.4, 75.3, 73.9, 73.2, 70.7, 69.5, 67.2; CH_0 δ 172.3, 171.5, 167.0, 159.3, 144.5, 144.4, 138.1, 130.9,

103.3, 81.5, 45.2; IR (neat) 3290, 2934, 1721, 1665, 1612, 1514, 1453, 1423, 1370, 1300, 1247, 1148, 1089, 1042, 894, 820, 737, 698, 637 cm^{-1}; HRMS (ESI) calcd for $C_{57}H_{74}NaO_{14}$ (M+Na) 1005.4976, found 1005.4984.

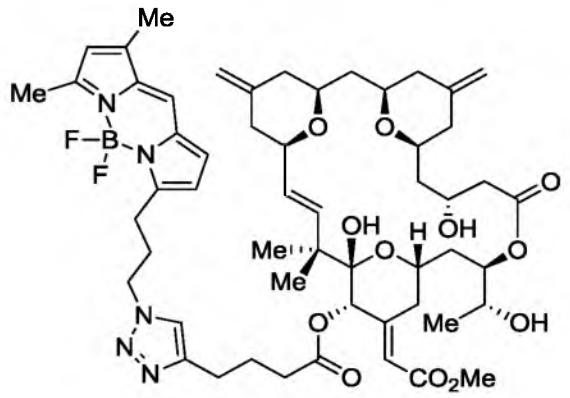


(1*R*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*, 21*R*,23*S*)-11,21-dihydroxy-17-((*R*)-1-hydroxyethyl)-13-(2-methoxy-2-oxoethylidene)-10,10 -dimethyl -5,25 -dimethylene -19-oxo -18,27,28,29 -tetraoxatetracyclo [21.3.1.$1^{3,7}$.$1^{11,15}$]nonacos-8-en-12-yl hex-5-ynoate (2.45): To a stirring solution of PMB ether **2.51** (6.4 mg, 0.0063 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) and H_2O (10 μL) at 0 °C in a 4 mL vial, was added DDQ (3 mg, 0.0126 mmol, 2.0 equiv). TLC analysis after 4 h at 0 °C indicated complete consumption of the PMB ether starting material. The reaction mixture was quenched by transfer into a 25 mL separatory funnel that contained a mixture of saturated $NaHCO_3$ solution (2 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was taken onto the next step without further purification

To a stirring solution of crude BOM ether in CH_3CN/ H_2O (25:1, 1 mL) in a 4 mL vial, was added $LiBF_4$ (24 mg, 0.252 mmol, 40.0 equiv). The reaction vial, was sealed and

the mixture was allowed to stir at 80 °C for 16 h. The reaction mixture was cooled to rt, quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 1.0 × 7.0 cm silica gel column, eluting with 25% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (4-10) were combined and concentrated under reduced pressure to yield macrolactone **2.45** (3.3 mg, 70%) as a white powder: $R_f = 0.37$ (40% EtOAc/hexanes); $[\alpha]_D^{20} = +8$ (c = 0.15, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.41-7.28 (m, 5H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.23 (d, *J* = 15.5 Hz, 1H), 5.95 (s, 1H), 5.60-5.55 (m, 1H), 5.34 (dd, *J* = 15.8, 8.8 Hz, 1H), 5.18 (s, 1H), 4.82 (ABq, *J* = 7.0 Hz, Δν = 14.5 Hz, 2H), 4.76 (s, 2H), 4.71 (s, 2H), 4.64 (ABq, *J* = 11.9 Hz, Δν = 24.2 Hz, 2H), 4.48 (s, 2H), 4.22-4.15 (m, 1H), 4.00-3.92 (m, 2H), 3.75 (s, 3H), 3.73-3.71 (m, 2H), 3.69 (s, 3H), 3.54-3.45 (m, 1H), 3.41-3.33 (m, 1H), 3.27-3.19 (m, 1H), 3.09 (s, 3H), 2.58 (dd, *J* = 15.0, 2.6 Hz, 1H), 2.51-2.42 (m, 2H), 2.32 (d, *J* = 12.4 Hz, 2H), 2.24 (td, *J* = 7.8, 2.6 Hz, 2H), 2.18 (t, *J* = 8.9 Hz, 2H), 2.15-2.02 (m, 2H), 2.00-1.92 (m, 4H), 1.91-1.79 (m, 4H), 1.77-1.59 (m, 2H), 1.56 (dd, *J* = 15.0, 7.8 Hz, 1H), 1.50-1.41 (m, 1H), 1.30-1.15 (m, 4H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.92-0.83 (m, 1H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.3, 171.5, 167.0, 159.3, 151.3, 144.5, 144.4, 141.8, 138.1, 130.9, 129.6, 128.6, 128.1, 127.8, 125.7, 119.5, 113.9, 109.1, 109.0, 103.3, 93.7, 83.1, 81.5, 77.4, 76.5, 76.4, 76.3, 75.3, 73.9, 73.2, 72.1, 70.7, 69.8, 69.5, 67.2, 55.4, 52.8, 51.4, 45.2, 44.2, 43.1, 41.9, 41.4, 41.1, 41.0, 40.9, 34.7, 33.3, 31.0, 29.9, 26.5, 23.3, 20.2, 17.9, 15.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 54.4, 52.8, 26.5, 20.2, 15.2; CH_2 δ 109.1, 109.0,

93.7, 72.1, 69.8, 44.2, 43.1, 41.9, 41.9, 41.4, 41.1, 41.0, 40.9, 34.7, 33.3, 31.0, 29.9, 23.4, 17.9; CH δ 141.8, 129.6, 128.1, 127.8, 125.7, 119.6, 113.9, 83.1, 81.5, 77.4, 76.5, 76.4, 76.3, 75.3, 73.9, 73.2, 70.7, 69.5, 67.2; CH_0 δ 172.3, 171.5, 167.0, 159.3, 144.5, 144.4, 138.1, 130.9, 103.3, 45.2; IR (neat) 2925, 1734, 1717, 1700, 1669, 1662, 1653, 1647, 1636, 1569, 1540, 1506, 1457, 1419, 1374, 1289, 1231, 1156, 1104, 1077, 1009, 890 cm^{-1}; HRMS (ESI) calcd for $C_{40}H_{56}NaO_{12}$ (M+Na) 751.8552, found 751.3685.



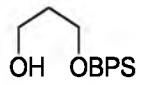
7-(3-(4-(4-(((1*R*,3*S*,7*R*,8*E*, 11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*S*)-11,21-dihydroxy-17-((*R*)-1-hydroxyethyl)-13-(2-meth oxy-2-oxoethylidene)-10,10-dimethyl-5,25-dimethylene -19-oxo-18,27,28,29 -tetraoxa tetracyclo [21.3.1.$1^{3,7}$.$1^{11,15}$] nonacos-8-en-12-yl)oxy) -4-oxobutyl) -1*H*-1,2,3-triazol-1-yl)propyl) -5,5-difluoro -1,3-dimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (Merle 44): To a stirring solution of alkyne **2.45** (2.7 mg, 0.0026 mmol, 1.0 equiv) and THF (1.0 mL) in a 4 mL reaction, was added freshly distilled (iPr)$_2$NEt (2 μg, 0.013 mmol, 5.0 equiv) and copper(I) iodide (2.5 mg, 0.013 mmol, 5.0 equiv). Azide **2.47** (2.4 mg, 0.0078 mmol, 3.0 equiv) was added to the suspension, the reaction vial, was sealed, and the mixture was allowed to stir at 70 ºC for 22 h. The reaction suspension was cooled to rt, filtered over a pad (4.0 × 0.5 cm) of Celite®, washed with copious amounts of Et_2O, and concentrated under reduced

pressure. Purification was accomplished by flash column chromatography using a 0.5 × 4.0 cm silica gel column, eluting with 1% MeOH/ CH_2Cl_2, collecting 1 mL fractions. The product containing fractions (7-13) were combined and concentrated under reduced pressure to yield Merle 44 (2.1 mg, 80%) as a red foam: R_f = 0.39 (60% EtOAc/hexanes); $[\alpha]_D^{20}$ = +10 (c = 0.06, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.11 (s, 1H), 6.89 (d, *J* = 3.9 Hz, 1H), 6.26 (d, *J* = 3.9 Hz, 1H), 6.14 (s, 1H), 5.98 (d, *J* = 2.0 Hz, 1H), 5.78 (d, *J* = 15.5 Hz, 1H), 5.32 (dd, *J* = 15.7, 8.9 Hz, 1H), 5.27 (s, 1H), 5.21 (ddd, *J* = 11.7, 8.6, 2.7 Hz, 1H), 5.14 (s, 1H), 4.76-4.67 (m, 4H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.41 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.21 (ddd, *J* = 13.7, 11.6, 2.4 Hz, 1H), 4.08-3.98 (m, 2H), 3.80 (ddd, *J* = 13.6, 7.7, 6.0 Hz, 1H), 3.71-3.69 (m, 1H), 3.68 (s, 3H), 3.56 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.52-3.46 (m, 1H), 3.44-3.37 (m, 1H), 3.03 (d, *J* = 7.4 Hz, 1H), 3.01 (d, *J* = 7.4 Hz, 1H), 2.79-2.69 (m, 2H), 2.58 (s, 3H), 2.50 (dd, *J* = 11.8, 2.2 Hz, 1H), 2.45 (dd, *J* = 11.8 1H), 2.43-2.34 (m, 3H), 2.27 (s, 3H), 2.21-1.78 (m, 14H), 1.73-1.48 (m, 5H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.12 (s, 3H), 1.00 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.5, 171.9, 167.2, 160.7, 157.0, 152.1, 144.0, 143.5, 138.9, 135.4, 130.2, 130.0, 128.4, 124.1, 120.7, 119.9, 117.0, 109.3, 108.8, 99.1, 80.2, 79.7, 77.8, 76.5, 74.5, 73.9, 70.6, 68.9, 64.7, 56.2, 51.3, 50.0, 45.0, 43.3, 42.8, 42.4, 41.5, 40.9, 40.3, 36.1, 34.1, 31.5, 29.9, 29.7, 29.6, 26.0, 24.6, 20.1, 15.2, 11.6; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.3, 29.6, 25.1, 20.1, 15.2, 11.6; CH_2 δ 109.3, 198.8, 50.0, 43.3, 42.8, 42.4, 41.5, 41.0, 40.9, 40.3, 36.1, 34.1, 31.5, 29.9, 29.7, 26.0, 24.6; CH δ 138.9, 130.0, 128.4, 124.1, 120.7, 119.9, 117.0, 80.2, 79.6, 68.9, 64.7; CH_0 δ 172.5 171.9, 167.2, 160.7, 157.0, 152.1, 144.0, 143.5, 133.4, 130.2, 99.1, 56.2, 45.0, 32.1; IR (neat) 3453, 3318, 2925, 2853, 1737, 1692, 1658, 1606, 1530, 1484,

1440, 1378, 1256, 1140, 1078, 985, 890 cm^{-1}; HRMS (ESI) calcd for $C_{54}H_{72}BF_2N_5NaO_{12}Si$ (M+Na) 1054.5136, found 1054.5155.

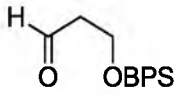
Experimental Procedures and Analytical Data for A-ring **2.16**

Compound **2.16** was previously prepared by Dr. Dennie Welch and are reported in his Ph.D. thesis and in the literature.[37] Since the compounds needed to construct 2.16 are not mentioned in this chapter, they are designated as **2.16.1-2.16.13**. A larger scale experimental procedure and analytical data for these compounds are reproduced here for those who may need to repeat this work.



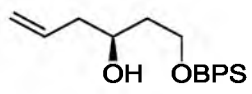
3-((*tert*-butyldiphenylsilyl)oxy)propan-1-ol (2.16.1).[37] To a stirring solution of 1,3-propanediol (78.0 mL, 1.08 mol, 4.4 equiv) and Et_3N (150 mL, 1.08 mol, 4.4 equiv) in CH_2Cl_2 (1.1 L) in a 2 L rb flask at 0 °C, was added *tert*-butyl(chloro)diphenylsilane (63.0 mL, 0.24 mol, 1.0 mmol). The solution was stirred at rt for 36 h. The reaction mixture was quenched by the addition of H_2O (500 mL), the phases were separated, and the aqueous phase was extracted with 50% EtOAc/hexanes (2 × 500 mL) then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 12.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (6-36) were combined and concentrated under reduced pressure to yield silyl ether **2.16.1** (72.3 g, 95%) as a clear yellow oil: R_f = 0.35 (30 % EtOAc/hexanes.); 500 MHz ^1H NMR ($CDCl_3$) δ 7.71–7.67 (m, 4H), 7.48–7.39 (m, 6H), 3.88–3.84 (m, 4H), 2.46 (t, J = 5.4 Hz, 2H), 1.82

(quin, J = 5.4 Hz, 2H), 1.07 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 135.6, 133.4, 129.9, 127.9, 63.1, 61.6, 34.4, 27.0, 19.2.



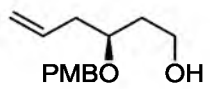
3-((*tert*-butyldiphenylsilyl)oxy)propanal (2.16.2).[37] To a stirring solution of oxalyl chloride (30.0 mL, 350.0 mmol, 1.5 equiv) in CH_2Cl_2 (1 L) in a 2 L rb flask at -78 °C, was added dimethyl sulfoxide (50.0 mL, 700 mmol, 3.0 equiv) slowly via an addition funnel. After 2 h at -78 °C, alcohol **2.16.1** (72.3 g, 233.3 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) was added dropwise via an addition funnel. The addition funnel was rinsed with additional CH_2Cl_2 (10 mL) and slowly added to the reaction mixture. After 1 h at -78 °C, Et_3N (163 mL, 1.17 mol, 5.0 equiv) was added to the reaction via an addition funnel. The solution was allowed to slowly reach rt over a 14 h period. The reaction mixture was then quenched by the addition of H_2O (500 mL) and stirred for 20 min. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 500 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 15.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (12-31) were combined and concentrated under reduced pressure to yield aldehyde **2.16.2** (71.0 g, 97%) as a white solid: R_f = 0.60 (30 % EtOAc/hexanes.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.83 (t, J = 2.0 Hz, 1H), 7.74–7.65 (m, 4H), 7.48-7.37 (m, 6H), 4.04 (t, J = 5.9 Hz, 2H), 2.62 (dt, J = 5.9, 2.0 Hz, 2H), 1.05 (s,

9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 202.1, 135.7, 133.4, 129.8, 127.9, 58.5, 46.5, 26.9, 19.3.



(*S*)-1-((*tert*-butyldiphenylsilyl)oxy)hex-5-en-3-ol (2.16.3).[37] To a stirring solution of oven dried 4 Å molecular sieves (105 g) and (*S*)-BINOL (14.1 g, 49.1 mmol, 0.22 equiv) in CH_2Cl_2 (480 mL) in a 2 L rb flask at rt, was added trifluoroacetic acid (90 μL, 0.9 mmol, 0.004 equiv) and Ti(O*i*Pr)$_4$ (1M in CH_2Cl_2, 25 mL, 24.6 mmol, 0.11 equiv) slowly via syringe. The reaction mixture was heated at reflux for 2 h, and then allowed to cool to rt. Aldehyde **2.16.2** (69.8 g, 223.4 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was added to the reaction flask via cannula. An additional CH_2Cl_2 (2 × 10 mL) rinse was used to transfer the remaining aldehyde residue into the reaction flask via cannula. Stirring continued for 30 min, then the solution was cooled to -78 °C and then allyltributyltin (90 mL, 290.4 mmol, 1.3 equiv) was added dropwise via syringe. The reaction mixture was stirred for an additional 30 min at -78 °C and then transferred to a -30 °C freezer. After 4 days, the reaction mixture was poured into a 3 L Erlenmeyer flask that contained an ice cold saturated aqueous $NaHCO_3$ solution (800 mL) and stirred for 30 min. The reaction mixture was filtered over a pad of Celite® and washed with copious amounts of CH_2Cl_2. The phases were separated, and the organic phase was washed with brine (2 × 500 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 15.0 cm silica gel column, eluting with 5% EtOAc/hexanes, collecting 125 mL fractions.

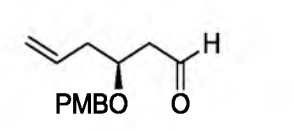
The product containing fractions (4-25) were combined and concentrated under reduced pressure. An additional purification was accomplished by flash column chromatography using a 10.0 × 10.0 cm silica gel column, eluting with 5% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (16-36) were combined and concentrated under reduced pressure to yield allyl alcohol **2.16.3** (71.7 g, 91%) as a clear oil: R_f = 0.50 (30 % EtOAc/hexanes.); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.71–7.67 (m, 4H), 7.48–7.39 (m, 6H), 5.87 (dddd, *J* = 17.6, 10.3, 7.3, 7.3 Hz, 1H), 5.16–5.08 (m, 2H), 4.01–3.95 (m, 1H), 3.92–3.82 (m, 2H), 3.23 (d, *J* = 2.5 Hz, 1H), 2.34–2.23 (m, 2H), 1.79–1.67 (m, 2H), 1.07 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 135.7, 135.1, 133.1, 130.0, 130.0, 128.0, 117.6, 71.1, 63.5, 42.2, 38.1, 27.0, 19.2; Assay of enantiomeric excess: HPLC (Chiralcel OD-H 25 cm column, 2.5% *i*PrOH/hexanes; 0.5 mL/min); t_r (major) = 8.13 min, t_r (minor) = 8.92 min; 98% ee



(*S*)-3-((4-methoxybenzyl)oxy)hex-5-en-1-ol (2.16.4).[37] To a stirring solution of alcohol **2.16.3** (61.9 g, 174.6 mmol, 1.0 equiv) and $Sc(OTf)_3$ (837 mg, 1.7 mmol, 0.01 equiv) in toluene (800 mL) in a 2L rb flask at 0° C, was added a solution of freshly prepared 4-methoxybenzyl trichloroacetimidate (74.0 g, 261.9 mmol, 1.5 equiv) in toluene (100 mL) dropwise via an addition funnel. The mixture was stirred at 0° C for 2 h then concentrated under reduced pressure. The reaction mixture was filtered over a pad of Celite®, washed with copious amounts of 10% EtOAc/hexanes, and then concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 15.0 cm silica gel column, eluting with 15% EtOAc/ hexanes, collecting 125 mL

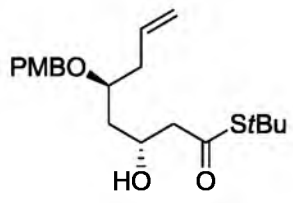
Erlenmeyer flask fractions. The product containing fractions (5-24) were combined and concentrated under reduced pressure to yield PMB ether as a clear yellow oil with inseparable impurities.

To a stirring solution of this crude PMB ether in THF (1.2 L) in a 2 L rb flask, was added tetrabutylammonium fluoride (1 M in THF, 230 mL, 227.0 mmol, 1.3 equiv). The reaction was allowed to proceed for 12 h at rt. The reaction mixture was quenched by transfer into a 2 L separatory funnel that contained a mixture of H_2O (300 mL) and 50% EtOAc/hexanes (300 mL). The phases were separated and the aqueous phase was extracted with 50% EtOAc/hexanes (2 × 300 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 × 12.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 125 mL Erlenmeyer flask fractions. The product containing fractions (7-21) were combined and concentrated under reduced pressure to yield alcohol **2.16.4** (24.7 g, 60%) as clear colorless oil: R_f = 0.25 (40 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.29-7.25 (m, 2H), 6.90-6.87 (m, 2H), 5.82 (dddd, J = 17.2, 10.2, 7.1, 7.1 Hz, 1 H), 5.12-5.08 (m, 2H), 4.51 (ABq, J = 11.2 Hz, Δν = 87.4 Hz, 2H), 3.81 (s, 3 H), 3.79-3.67 (m, 3H), 2.50-2.26 (m, 2H), 1.86-1.71 (m, 2H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 159.4, 134.4, 130.4, 129.6, 117.7, 114.0, 77.7, 70.8, 60.8, 55.4, 38.2, 36.1.



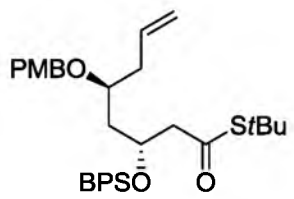
(*S*)-3-((4-methoxybenzyl)oxy)hex-5-enal (2.16.5).[37] To a stirring solution of alcohol **2.16.4** (24.7 g, 93.8 mmol, 1.0 equiv) in CH_2Cl_2 (1 L) in a 2 L rb flask at -5° C,

was added (iPr)$_2$NEt (115 mL, 656.6 mmol, 7.0 equiv) and DMSO (67 mL, 938.1 mmol, 10.0 equiv). Stirring continued for 10 min at -5° C, then SO_3•Py (59.7 g, 375.2 mmol, 4.0 equiv) was added in three portions over 15 min. Stirring continued for 1 h at -5° C, then the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (300 mL). The phases were separated and the aqueous phase was extracted with 50% EtOAc/hexanes (2 × 500 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 x 15.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (10-25) were combined and concentrated under reduced pressure to yield aldehyde **2.16.5** (20.7 g, 85%) as a clear yellow oil: R_f = 0.44 (50 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.77 (t, J = 2.0 Hz, 1H), 7.28-7.23 (m, 2H), 6.91 -6.86 (m, 2H), 5.81 (dddd, J = 16.8, 9.6, 7.3, 7.3 Hz, 1 H), 5.15-5.14 (m, 1H), 5.12 (s, 1H), 4.51 (ABq, J = 8.2 Hz, Δν = 49.0 Hz, 2H), 4.02 (dddd, J= 7.8, 6.9, 4.9, 4.9 Hz, 1H), 3.81 (s, 3 H), 2.67 (ddd, J = 16.6, 7.9, 2.5 Hz, 1H), 2.56 (ddd, J = 16.6, 4.5, 1.5 Hz, 1H), 2.48-2.41 (m, 1H), 2.40-2.33 (m, 1H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 201.5, 159.4, 133.7, 130.2, 129.5, 118.3, 113.9, 73.4, 71.0, 55.4, 48.1, 38.4.



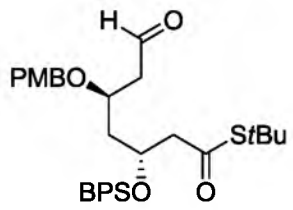
(3*R*,5*S*)-*S*-*tert*-butyl 3-hydroxy-5-((4-methoxy benzyl)oxy)oct-7-enethioate (2.16.6).[37] To a stirring solution of aldehyde **2.16.5** (7.63 g, 31.9 mmol, 1.0 equiv) in

toluene (300 mL) in a 1 L round bottom flask under an atmosphere of Ar at -78 °C, was added a freshly prepared solution of $TiCl_2(O\textit{i}Pr)_2$ (1 M in toluene, 80.0 mL, 79.7 mmol, 2.5 equiv) dropwise via cannula. The resulting solution was allowed to stir for 15 min, then a solution of ((1-(*tert*-butylthio)vinyl)oxy)trimethylsilane (16.9 g, 82.9 mmol, 2.6 equiv) in toluene (50 mL) was added dropwise via cannula over a 10 min period. After 4 h at -78 °C, the reaction mixture was poured into a 2 L Erlenmeyer flask that contained aqueous pH 7 buffer solution (200 mL) and stirred for 20 min. The suspension was filtered over a pad of Celite® and washed with copious amounts of CH_2Cl_2. The layers were separated and the organic layer was washed with saturated aqueous NH_4Cl solution (200 mL) and brine (200 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 10.0 x 15.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 125 mL fractions. The product containing fractions (6-21) were combined and concentrated under reduced pressure to yield alcohol **2.16.6** (11.0 g, 94%) as a clear yellow oil: R_f = 0.45 (30 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.30-7.25 (m, 2H), 6.91-6.86 (m, 2H), 5.81 (dddd, J = 17.3, 10.2, 7.2, 7.2 Hz, 1 H), 5.15 -5.06 (m, 2H), 4.51 (ABq, J = 11.0 Hz, Δν = 70.9 Hz, 2H), 4.33-4.26 (m, 1H), 3.81 (s, 3 H), 3.82-3.75 (m, 1H), 3.18 (d, J = 4.1 Hz, 1H), 2.61 (d, J = 2.5 Hz, 1H), 2.59 (s, 1H), 2.47-2.39 (m, 1H), 2.37-2.30 (m, 1H), 1.70-1.55 (m, 2H), 1.47 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 200.0, 159.4, 134.4, 130.5, 129.7, 117.9, 114.0, 75.4, 71.2, 65.9, 55.4, 51.5, 48.5, 40.2, 38.4, 29.9.



(3*R*,5*S*)-*S*-*tert*-butyl 3-((*tert*-butyldiphenylsilyl)oxy) -5-((4-methoxybenzyl) oxy)oct-7-enethioate (2.16.7).[37] To a stirring solution of alcohol **2.16.6** (5.34 g, 14.6 mmol, 1.0 equiv) and imidazole (2.98 g, 43.7 mol, 3.0 equiv) in DMF (40 mL) in a 100 ml rb flask at rt, was added *tert*-butyl(chloro)diphenylsilane (5.7 mL, 21.9 mmol, 1.5 equiv). The reaction was allowed to proceed for 36 h at rt, after which time TLC analysis indicated complete consumption of the alcohol starting material. The reaction mixture was quenched by transfer into a 250 mL separatory funnel that contained a mixture of saturated aqueous $NaHCO_3$ solution (50 mL) and diluted with 50% EtOAc/hexanes (50 mL). The phases were separated, and the aqueous phase was extracted with 50% EtOAc/hexanes (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 6.0 × 20.0 cm silica gel column, eluting with 5% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (16-42) were combined and concentrated under reduced pressure to yield silyl ether **2.16.7** (7.9 g, 95%) as a clear oil: R_f = 0.49 (20 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.76-7.66 (m, 4H), 7.44-7.34 (m, 6H), 7.14-7.09 (m, 2H), 6.84-6.81 (m, 2H), 5.58 (dddd, *J* = 14.2, 10.7, 7.3, 7.3 Hz, 1 H), 4.98-4.92 (m, 2H), 4.40 (tt, *J* = 5.9, 5.9 Hz, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 4.02 (d, *J* = 10.6 Hz, 1H), 3.81 (s, 3 H), 3.34 (dddd, *J* = 5.9, 5.9, 5.2, 5.2 Hz, 1 H), 2.71 (dd, *J* = 14.7, 6.3 Hz, 1 H), 2.64 (dd, *J* = 14.7, 5.9 Hz, 1 H), 2.13-2.02 (m, 2H), 1.74 (ddd, *J* = 14.2, 8.3, 5.9 Hz, 1 H), 1.65 (ddd, *J* = 14.2, 6.4, 3.9 Hz, 1 H), 1.43 (s, 9H), 1.04 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 198.0, 164.2, 136.2,

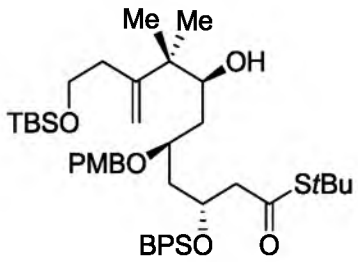
136.1, 134.0, 134.5, 134.2, 131.0, 129.9, 129.8, 127.8, 127.7, 117.3, 113.8, 75.7, 70.3, 69.2, 55.5, 53.0, 48.1, 42.4, 38.6, 30.0, 27.2, 19.6.



(3*R*,5*R*)-*S*-*tert*-butyl 3-((*tert*-butyldiphenylsilyl) oxy)-5-((4-methoxybenzyl)oxy)-7-oxoheptanethioate (2.16.8).[37] To a stirring solution of olefin **2.16.7** (7.9 g, 13.1 mmol, 1.0 equiv) and 4-methylmorpholine-*N*-oxide (4.6 g, 39.2 mmol, 3.0 equiv) in THF/*t*-BuOH/H_2O (4:4:1, 135 mL) in a 250 ml rb flask at rt, was added a solution of OsO_4 (0.08 M in THF, 16 mL, 1.3 mmol, 0.1 equiv) dropwise. The reaction was allowed to proceed for 14 h at rt, after which time TLC analysis indicated complete consumption of the olefin starting material. The reaction mixture was quenched by pouring the mixture into a 1 L Erlenmeyer flask that contained saturated aqueous $Na_2S_2O_3$ solution (250 mL) and EtOAc (250 mL). The phases were separated, then the aqueous phase was extracted with EtOAc (2 × 200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude diol.

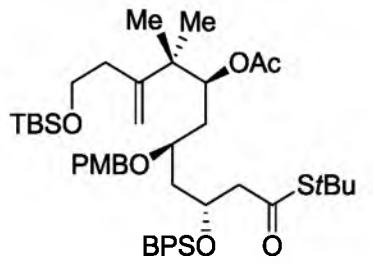
To a stirring solution of the crude diol in benzene (50 mL) was added lead(II) acetate (4.5 g, 13.7 mmol, 1.05 equiv). The suspension was stirred for 1.5 h and then filtered over a pad of Celite®, washing with copious amounts of hexanes. After concentration of the filtrate under reduced pressure, purification was accomplished by flash column chromatography using a 5.0 × 25.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (40-80) were combined and

concentrated under reduced pressure to yield aldehyde **2.16.8** (6.0 g, 76%) as clear colorless oil: R_f = 0.36 (20 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ **9**.54 (t, *J* = 2.0 Hz, 1 H), 7.73-7.76 (m, 4H), 7.48-7.34 (m, 6H), 7.12-7.06 (m, 2H), 6.86-6.80 (m, 2H), 4.33 (tt, *J* = 6.3, 5.9 Hz, 1H), 4.19 (ABq, *J* = 10.7 Hz, Δν = 41.8 Hz, 2H), 3.85-3.81 (m, 1H), 3.80 (s, 3 H), 2.72 (dd, *J* = 14.2, 5.9 Hz, 1 H), 2.62 (dd, *J* = 14.7, 6.3 Hz, 1 H), 2.34 (ddd, *J* = 16.6, 6.8, 2.4 Hz, 1 H), 2.36 (ddd, *J* = 16.1, 4.9, 2.0 Hz, 1 H), 1.96 (ddd, *J* = 13.7, 7.3, 5.9 Hz, 1 H), 1.64 (ddd, *J* = 14.2, 5.9, 5.9 Hz, 1 H), 1.43 (s, 9H), 1.05 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 201.2, 197.7, 159.4, 136.1, 136.0, 133.6, 133.8, 130.4, 130.0, 130.0, 129.5, 127.9, 113.9, 71.4, 70.7, 68.5, 55.5, 52.6, 48.6, 48.3, 42.8, 29.9, 27.1, 19.6.



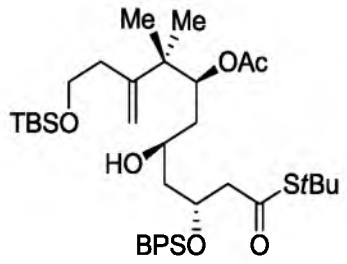
(3*R*,5*S*,7*S*)-S-*tert*-butyl 11-((*tert*-butyl dimethyl silyl)oxy)-3-((*tert*-butyldiphenylsilyl)oxy)-7-hydroxy-5-((4-methoxybenzyl) oxy)-8,8-di methyl-9-methyleneundecanethioate (2.16.9).[37] To a stirring solution of aldehyde **2.16.8** (1.74 g, 2.87 mmol, 1.0 equiv) in toluene (30 mL) in a 100 ml rb flask at -78 °C, was added a freshly prepared Me_2AlCl (3 M in toluene, 6.7 mL, 20.1 mmol, 7.0 equiv) dropwise via syringe down the side of the flask. This was followed by an addition of *tert*-butyl-dimethyl-(3-methyl-tributyl-stannanyl-methyl-pent-enyloxy)-silane[37] (2.08 g, 4.01 mmol, 1.4 equiv) in toluene (6 mL) via cannula down the inside of the reaction flask over a 10 min period. The reaction was allowed to proceed for 1 h at -78 °C, after which time TLC analysis indicated

complete consumption of the aldehyde starting material. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), and then poured into a 1 L Erlenmeyer flask that contained aqueous sodium potassium tartrate salt solution (200 mL) and 20% EtOAc/hexanes (200 mL). This mixture was stirred for 12 h. The phases were separated and the aqueous phase was extracted with 20% EtOAc/hexanes (2 × 200 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 3.0 x 13.0 cm silica gel column, eluting with 5% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (16-42) were combined and concentrated under reduced pressure to yield alcohol **2.16.9** (2.0 g, 87%) as a clear yellow oil: R_f = 0.57 (30 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.76-7.69 (m, 4H), 7.46-7.34 (m, 6H), 7.12-7.16 (m, 2H), 6.86-6.81 (m, 2H), 4.99 (s, 1H), 4.92 (s, 1H), 4.33 (quin, J = 5.9, 1H), 4.23 (ABq, J = 10.7 Hz, Δν = 50.1 Hz, 2H), 3.81 (s, 3H), 3.80-3.76 (m, 2H), 3.70-3.65 (m, 1H), 3.64-3.58 (m, 1H), 2.71 (dd, J = 14.7, 6.4 Hz, 1H), 2.65 (dd, J = 14.7, 5.9 Hz, 1H), 2.43 (d, J = 2.9 Hz, 1H), 2.32-2.17 (m, 2H), 1.96 (ddd, J = 14.2, 6.8, 6.8 Hz, 1H), 1.59 (td, J = 13.7, 5.9 Hz, 1H), 1.46 (s, 9H), 1.27-1.14 (m, 2H), 1.06 (s, 9H), 0.97 (s, 3H), 0.95 (s, 3H), 0.92 (s, 9H), 0.89 (s, 3H), 0.87 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.8, 159.2, 151.8, 136.2, 136.1, 134.0, 134.2, 133.9, 130.9, 129.9, 129.8, 129.6, 127.8, 127.8, 113.8, 111.3, 74.5, 71.6, 71.0, 68.9, 63.5, 55.4, 52.4, 48.1, 43.9, 42.6, 35.5, 34.0, 30.0, 27.1, 26.2, 22.7, 21.6, 19.6, 18.6, -5.0, -5.1.



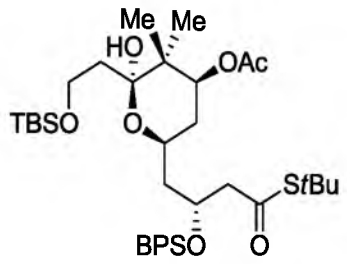
(5*R*,7*S*,9*S*)-5-(2-(*tert*-butylthio)-2-oxo ethyl)-7-((4-methoxybenzyl)oxy)-2,2,10,10,15,15,16,16-octamethyl-11-methylene-3,3-diphenyl-4, 14-dioxa-3,15-disilaheptadecan-9-yl acetate (2.16.10).[37] To a stirring solution of alcohol **2.16.9** (4.43 g, 5.30 mmol, 1.0 equiv) and DMAP (61 mg, 0.50 mmol, 0.1 equiv) in CH_2Cl_2 (50 mL) in a 250 ml rb flask at 0 °C, was added a mixture of acetic anhydride (1.0 mL, 10.6 mmol, 2.0 equiv) and Et_3N (2.2 mL, 15.9 mol, 3.0 equiv) dropwise via syringe. The solution was stirred at rt for 16 h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (50 mL) and stirred for 1 h. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 5.0 × 15.0 cm silica gel column, eluting with 5% EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (36-65) were combined and concentrated under reduced pressure to yield ester **2.16.10** (4.6 g, 99%) as a clear oil: R_f = 0.54 (20 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74-7.66 (m, 4H), 7.46-7.32 (m, 6H), 7.24-7.16 (m, 2H), 6.86-6.80 (m, 2H), 5.29 (d, *J* = 8.9 Hz, 1H), 4.91 (s, 1H), 4.84 (s, 1H), 4.30-4.15 (m, 4H), 3.80 (s, 3H), 3.79-3.78 (m, 1H), 3.68 (t, *J* = 7.3 Hz, 2H), 3.26-3.18 (m, 1H), 2.66 (dd, *J* = 14.7, 6.4 Hz, 1H), 2.56 (dd, *J* = 14.7, 2.9 Hz, 1H), 2.33-2.17 (m, 2H), 2.00 (s, 3H), 1.96-1.90 (m, 1H), 1.33-1.17 (m, 2H), 1.46 (s, 9H), 1.36-1.20 (m, 2H), 1.06 (s, 9H), 0.97 (s, 3H), 0.95 (s, 3H), 0.91 (s, 9H), 0.05 (s, 6H); 125 MHz ^{13}C

NMR ($CDCl_3$) δ 197.7, 170.8, 159.1, 150.9, 136.1, 136.0, 133.9, 133.8, 131.1, 129.9, 129.8, 129.7, 127.8, 127.8, 113.8, 111.2, 74.6, 73.4, 71.3, 68.7, 63.3, 55.4, 52.3, 48.2, 43.4, 42.8, 35.8, 34.7, 30.0, 27.1, 26.2, 24.1, 21.6, 21.3, 19.5, 18.4, -5.1, -5.0.



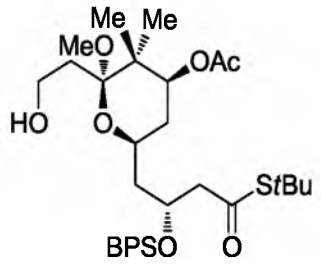
(5*R*,7*S*,9*S*)-5-(2-(*tert*-butylthio)-2-oxoethyl)-7-hydroxy-2,2,10,10,15,15,16,16-octamethyl-11-methylene-3,3-diphenyl-4,14-dioxa-3,15-disilaheptadecan-9-yl acetate (2.16.11).[37] To a stirring solution of the PMB ether **2.16.10** (4.61 g, 5.26 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) in a 250 ml rb flask at rt, was added pH 7 phosphate buffer (20 mL). DDQ (2.40 g, 10.5 mmol, 2.0 equiv) was added in one portion and the mixture was stirred vigorously for 3 h. The reaction mixture was quenched by transfer into a 1 L separatory funnel that contained a mixture of 50% EtOAc/hexanes (300 mL) and saturated aqueous $NaHCO_3$ solution (300 mL). The phases were separated, and the aqueous phase was extracted with 50% EtOAc/hexanes (2 × 300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 5.0 × 15.0 cm silica gel column, eluting with 10 % EtOAc/hexanes, collecting 25 mL fractions. The product containing fractions (12-24) were combined and concentrated under reduced pressure to yield alcohol **2.16.11** (3.57 g, 90%) as a clear oil: R_f = 0.55 (20 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74–7.66 (m, 4H), 7.47–7.36 (m, 6H), 5.07 (dd, *J* = 10.7, 1.0 Hz, 1H), 4.94 (s, 1H), 4.87 (s, 1H),

4.45–4.36 (m, 1H), 3.77–3.66 (m, 1H), 3.52–3.45 (m, 1H), 2.66–2.62 (m, 3H), 2.26 (t, J = 7.3 Hz, 2H), 1.93 (s, 3H), 1.64–1.51 (m, 2H), 1.41 (s, 9H), 1.38–1.22 (m, 3H), 1.04 (s, 9H), 1.02 (s, 3H), 1.01 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.7, 172.2, 150.6, 136.1, 136.0, 133.8, 129.9(×2), 127.9, 127.8, 111.3, 75.2, 68.5, 63.8, 63.3, 52.5, 48.1, 44.4, 42.9, 38.1, 34.7, 29.9, 27.1, 26.1, 24.1, 22.0, 21.0, 19.6, 18.5, -5.1.



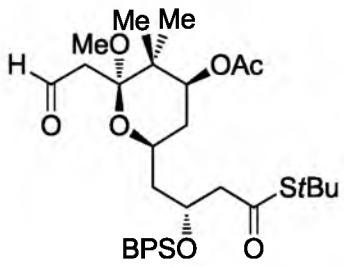
(2*S*,4*S*,6*S*)-6-((*R*)-2-((*tert*-butyldiphenyl silyl) oxy)-4-(*tert*-butylthio)-4-oxobutyl)-2-(2-hydroxyethyl)-2-methoxy-3,3-dimethyl tetra hydro-2*H*-pyran -4-yl acetate (2.16.12).[37] To a stirring solution of alkene **2.16.11** (3.57 g, 4.71 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added $NaHCO_3$ (3.96 g, 47.2 mmol, 10.0 equiv). The reaction mixture was cooled to -78° C and O_3 was bubbled through the mixture until the solution developed a light blue color. The excess O_3 was purged from the reaction mixture by bubbling O_2 through it for 20 min. Dimethyl sulfide (6.9 ml, 94.2 mmol, 20.0 equiv) was added to the mixture dropwise via syringe. The solution was slowly allowed to reach rt overnight. The solid $NaHCO_3$ was removed by filtration, and the solution was concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 5.0 × 12.0 cm silica gel column, eluting with 5% EtOAc/hexanes, collecting 25 mL Erlenmeyer flask fractions. The product containing fractions (10-46) were combined and concentrated under reduced pressure to yield hemiketal **2.16.12** (2.94 g, 82%) as clear

colorless oil: R_f = 0.40 (10 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.75-7.66 (m, 4H), 7.47-7.35 (m, 6H), 5.23 (s, 1H), 5.09 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.28 (quin, *J* = 5.9, 1H), 4.18 (t, *J* = 10.3 Hz, 1H), 3.85-3.78 (m, 1H), 3.76-3.71 (m, 1H), 2.70 (d, *J* = 5.9 Hz, 2H), 2.68-2.63 (m, 1H), 2.02 (s, 3H), 1.94-1.84 (m, 1H), 1.73 (dt, *J* = 14.2, 7.8 Hz, 1H), 1.56-1.50 (m, 1H), 1.45 (s, 9H), 1.38-1.32 (m, 1H), 1.04 (s, 9H), 0.92 (s, 3H), 0.90 (s, 9H), 0.83 (s, 3H), 0.10 (s, 6H),; 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.9, 170.5, 136.1(×2), 134.6, 134.4, 129.9, 129.7, 127.8, 127.7, 102.3, 73.4, 69.3, 64.7, 60.3, 34.1, 33.5, 30.0, 27.2, 26.0, 21.4, 21.2, 19.6, 18.2, 16.8, -5.2, -5.4.



(2*S*,4*S*,6*S*)-6-((*R*)-2-((*tert*-butyldiphenylsilyl) oxy)-4-(*tert*-butylthio)-4-oxobutyl)-2-(2-hydroxyethyl)-2-methoxy-3,3-dimethyltetra hydro-2*H*-pyran -4-yl acetate (2.16.13).[37] To a stirring solution of TBS ether **2.16.12** (813 mg, 1.07 mmol, 1.0 equiv) in MeOH (10 mL) in a 25 ml rb flask, was added (±)-camphor-10-sulfonic acid (62 mg, 0.268 mmol, 0.25 equiv) at 0 ° C. Stirring continued for 2 h at 0 ° C, then the reaction was quenched by pipetting into a stirring saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 3.0 × 10.0 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 8 mL fractions. The product containing

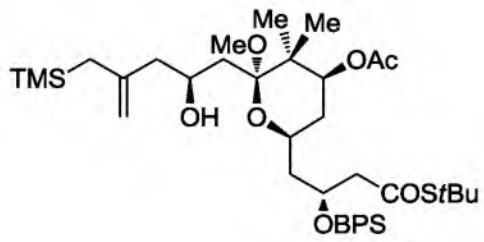
fractions (30-55) were combined and concentrated under reduced pressure to yield alcohol **2.16.13** (637 mg, 90%) as a clear oil: R_f = 0.33 (30 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72–7.62 (m, 4H), 7.45–7.35 (m, 6H), 5.05 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.28 (q, *J* = 5.9, 1H), 3.68– 3.57 (m, 2H), 3.46 (dddd, *J* = 11.7, 7.8, 4.4, 3.3 Hz, 1H), 2.96 (s, 3H), 2.72 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.63 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.39 (s, 1H), 2.01 (s, 3H), 1.99–1.95 (m, 1H), 1.84–1.72 (m, 1H), 1.53 – 1.45 (m, 2H), 1.14–1.02 (m, 10H), 1.04 (s, 9H), 0.90 (s, 3H), 0.82 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.9, 170.6, 136.1, 133.9, 130.0, 127.9, 104.9, 73.4, 68.7, 65.9, 59.6, 52.5, 48.6, 48.3, 43.8, 41.9, 34.7, 32.9, 29.9, 27.1, 21.3, 20.5, 19.4, 17.2.



(2*S*,4*S*,6*S*)-6-((*R*)-2-((*tert*-butyldiphenylsilyl) oxy) -4-(*tert*-butylthio)-4-oxobutyl)-2-methoxy-3,3-dimethyl-2-(2-oxoethyl)tetra hydro-2*H*-pyran-4-yl acetate (2.16).[37] To a stirring solution of alcohol **2.16.13** (637 mg, 0.967 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) in a 100 ml rb flask at -5° C, was added (*i*Pr)$_2$NEt (1.2 mL, 6.77 mmol, 7.0 equiv) and DMSO (0.7 mL, 9.67 mmol, 10.0 equiv). Stirring continued for 10 min at -5° C, and then SO_3•Py (616 mg, 3.87 mmol, 4.0 equiv) was added in one portion. Stirring continued for 1 h at -5° C, then the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried

over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 3.0 × 12.0 cm silica gel column, eluting with 10% EtOAc/ hexanes, collecting 8 mL fractions. The product containing fractions (4-20) were combined and concentrated under reduced pressure to yield aldehyde **2.16** (522 mg, 82%) as a white foam: R_f = 0.45 (20 % EtOAc/Hex.); 500 MHz ^{1}H NMR ($CDCl_3$) δ **9.65** (t, *J* = 2.9 Hz, 1H), 7.71–7.62 (m, 4H), 7.46–7.35 (m, 6H), 5.01 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.28 (q, *J* = 6.3, 1H), 3.41 (dddd, *J* = 11.7, 7.8, 4.4, 3.4 Hz, 1H), 3.00 (s, 3H), 2.72 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.63 (dd, *J* = 14.2, 5.2 Hz, 1H), 2.52 (t, *J* = 2.9 Hz, 2H), 2.01 (s, 3H), 1.77 (ddd, *J* = 14.6, 7.8, 6.8 Hz, 1H), 1.50 (ddd, *J* = 14.2, 4.4, 4.4 Hz, 2H), 1.43 (s, 9H), 1.16–1.06 (m, 1H), 1.03 (s, 9H), 0.87 (s, 3H), 0.82 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 201.4, 197.9, 170.6, 136.1, 134.1, 130.0, 127.9, 104.0, 72.8, 69.1, 66.4, 53.0, 48.8, 48.3, 45.8, 43.5, 42.0, 32.8, 29.9, 27.1, 21.3, 20.8, 19.5, 17.4.

Experimental Procedures and Analytical Data for Tricyclic Core **2.70**

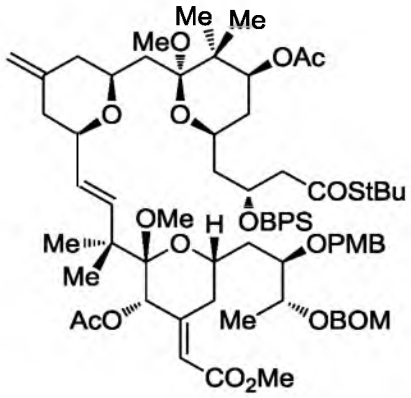


(2*S*,4*S*,6*S*)-6-((*R*)-2-((*tert*-butyl diphenylsilyl)oxy)-4-(*tert*-butylthio)-4-oxobutyl)-2-((*S*)-2-hydroxy-4-((trimethylsilyl) methyl)pent-4-en-1-yl)-2-methoxy-3,3-dimethyl tetrahydro-2*H*-pyran-4-yl acetate (2.63).[31] A 5 ml rb flask, was charged with *N*,*N*'-((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(4-methyl benzenesulfon amide) (373 mg, 0.717 mmol, 3.0 equiv) and heated to 90 °C under 0.2 mm Hg vacuum. After 18 h, the dry powder

was cooled to rt, and the flask was flushed with Ar. CH_2Cl_2 (2 mL) was added via syringe and the suspension was cooled to 0 °C. Boron tribromide (68 μL, 0.717 mmol, 3.0 equiv) was added dropwise via syringe and then stirred for 1 h at rt. The solvent was removed under high vacuum and the flask was then purged with Ar. A mixture of trimethyl(2-((tributyl stannyl)methyl) allyl)silane (299 mg, 0.717 mmol, 3.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (147 mg, 0.282 mmol, 3.0 equiv) and in CH_2Cl_2 (1.5 mL + 0.5 mL rinse) was added via cannula. Stirring continued for 16 h under Ar.

To a stirring solution of aldehyde **2.16** (157 mg, 0.239 mmol, 1.0 equiv) and CH_2Cl_2 (5 mL) at -78 °C in a 15 ml rb flask, was added the previously prepared solution of (4*S*,5*S*)-4,5-diphenyl-1,3-ditosyl-2-(2-((trimethylsilyl)methyl)allyl)-1,3,2-diazaborolidine dropwise via cannula. TLC analysis after 2 h at -78 °C indicated complete consumption of the aldehyde starting material. The mixture was quenched by the addition of pH 7 aqueous buffer (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Et_2O/ hexanes (15 mL of 2:1) was added, *N*,*N*'-((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfon amide) was recovered via filtration, and the solid was washed with copious amounts of 2:1 Et_2O/hexanes. The filtrate was concentrated under reduced pressure and purification was accomplished by flash column chromatography using a 3.0 × 16.0 cm silica gel column, eluting with 5% EtOAc/ hexanes, collecting 8 mL fractions. The product containing fractions (31-43) were combined and concentrated under reduced pressure to yield silane **2.63** (167 mg, 89%) as a 10:1 mixture of diastereomers as measured by NMR: R_f = 0.60 (20% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74-7.64 (m, 4H), 7.46-7.34 (m, 6H), 5.04 (dd, *J* = 11.7, 4.9 Hz, 1H),

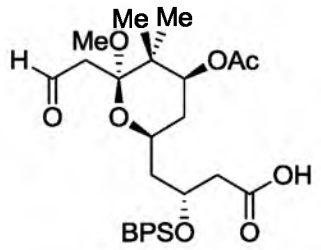
4.68-4.60 (m, 2H), 4.27 (ddd, J = 12.2, 5.9, 5.9 Hz, 1H), 4.08 (ddd, J = 12.2, 5.9, 5.9 Hz, 1H), 3.52-3.42 (m, 1H), 3.14 (s, 3H), 2.73 (dd, J = 14.6, 5.4, 1H), 2.64 (dd, J = 14.6, 5.4 Hz, 1H), 2.19 (dd, J = 13.7, 6.4 Hz, 1H), 2.02 (s, 3H), 1.95 (dd, J = 13.2, 6.8 Hz, 1H), 1.82-1.77 (m, 2H), 1.55 (d, J = 1.5 Hz, 2H), 1.44 (s, 9H), 1.08 (s, 9H), 1.04 (s, 9H), 0.91 (s, 3H), 0.83 (s, 3H), 0.04 (s, 9H) ; 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.8, 170.7, 144.4, 136.1, 136.0, 135.0, 130.0, 129.9, 129.8, 127.9(×2), 110.3, 104.9, 73.2, 68.8, 67.1, 66.4, 52.7, 49.1, 48.4, 46.2, 43.9, 39.6, 32.8, 30.0, 27.1, 21.4, 19.5, -1.1.



(*E*)-methyl 2-((2*S*,3*S*,6*S*)-3-acetoxy-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*S*)-4-acetoxy-6-((*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-4-(*tert*-butyl thio)-4-oxobutyl)-2-methoxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl) methyl)-4-methyl enetetrahydro-2*H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-6-((2*R*,3*R*)-3-((benzyloxy) methoxy)-2-((4-methoxybenzyl) oxy)butyl)-2-methoxydihydro-2*H*-pyran-4(3*H*)-ylidene) acetate (2.70).[31] To a stirring solution of aldehyde **2.25** (111 mg, 0.166 mmol, 1.0 equiv) and hydroxyallysilane **2.63** (143 mg, 0.182 mmol, 1.1 equiv) in Et_2O (4 mL) in a 15 ml rb flask at -78 °C, was added a solution of TMSOTf (0.9 M in Et_2O, 150 µL, 0.200 mmol, 1.2 equiv) dropwise via syringe down the side of the flask. Stirring continued for 1 h at -78° C, then the reaction

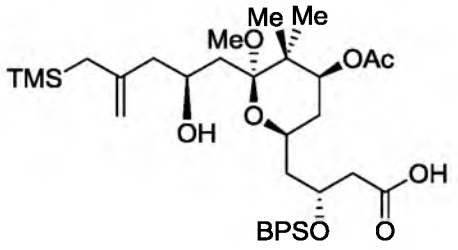
mixture was quenched by the addition of (iPr)$_2$NEt (0.2 mL) followed by saturated aqueous $NaHCO_3$ solution (3.0 mL). The reaction mixture was allowed to then reach rt. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 3.0 x 22.0 cm silica gel column, eluting with 25% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (21-48) were combined and concentrated under reduced pressure to yield pyran **2.70** (124 mg, 55%) as a clear oil: R_f = 0.43 (30 % EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.65 (m, 4H), 7.46-7.30 (m, 11H), 7.18-7.23 (m, 2H), 6.86-6.82 (m, 2H), 6.00 (dd, J = 16.1, 1.5 Hz, 1H), 5.89 (s, 1H), 5.45 (s, 1H), 5.39-5.31 (m, 1H), 4.95 (dd, J = 11.7, 5.4 Hz, 1H), 4.85 (d, J = 2.0 Hz, 2H), 4.70 (s, 1H), 4.67 (s, 2H), 4.61(d, J = 10.7 Hz, 1H), 4.42 (d, J = 10.7 Hz, 1H), 4.28-4.22 (m, 1H), 4.15-4.00 (m, 2H), 3.88 (ddd, J = 9.6, 4.4, 2.0 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.66-3.61 (m, 1H), 3.51-3.44 (m, 1H), 3.34-3.35 (m, 1H), 3.24 (s, 3H), 3.22-3.14 (m, 1H), 2.94 (s, 3H), 2.73-2.69 (m, 2H), 2.38-2.10 (m, 3H), 2.06 (s, 3H), 2.04-2.x 02 (m, 2H), 1.99 (s, 3H), 1.96-1.79 (m, 5H), 1.76-1.62 (m, 4H), 1.45 (s, 9H), 1.22 (d, J = 6.3 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.03 (s, 9H), 0.88 (s, 3H), 0.83 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 198.2, 170.7, 169.4, 166.7, 159.4, 152.6, 144.7, 138.1, 137.8, 136.2, 136.0, 134.4, 133.7, 130.7, 130.0, 129.9, 129.5 (×2), 128.7, 128.0, 127.9, 127.8 (×2), 126.5, 117.2, 114.0 (×2), 104.1, 102.8, 93.6, 78.6, 77.4, 74.8, 74.4, 73.8, 72.5, 72.1, 68.5, 66.1, 55.5, 53.2, 51.5, 51.3, 48.5, 48.2, 46.2, 43.7, 42.1, 40.6, 39.1, 36.5, 32.8, 30.1, 30.0, 27.1, 24.3, 24.0, 21.5, 21.4, 20.7, 19.6, 16.7, 14.9.

Experimental Procedures and Analytical Data for Macrolactone **2.79**



(*R*)-4-((2*S*,4*S*,6*S*)- 4-acetoxy- 6-methoxy-5,5-dimethyl-6-(2-oxoethyl)tetra hydro-2*H*-pyran-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy) butanoic acid (2.71). To a stirring solution of thioester **2.16** (175 mg, 0.266 mmol, 1.0 equiv) in THF/H_2O (5:1, 3 mL) in a 15 ml rb flask at rt, was added *N*-bromosuccidimide (142 mg, 3.0 equiv) in a single portion. TLC analysis after 2 h indicated complete consumption of the thioester starting material. The mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL) and diluted with EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2.0 × 8.0 cm silica gel column, eluting with 3% MeOH/17% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (25-48) were combined and concentrated under reduced pressure to yield acid **2.71** (135 mg, 87%) as a white foam: R_f = 0.50 (5:4:1 hexanes: EtOAc: MeOH); $[\alpha]_D^{20}$ = +21.0 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ **9.65** (t, *J* = 3.4 Hz, 1H), 7.72-7.62 (m, 4H), 7.48-7.34 (m, 6H), 5.02 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.23 (dddd, *J* = 6.4, 6.4, 4.8, 4.8 1H), 3.40 (dddd, *J* = 11.7, 7.3, 3.9, 3.9 Hz, 1H), 2.99 (s, 3H), 2.60 (dd, *J* = 10.7, 4.9 Hz, 1H), 2.55 (t, *J* = 3.4 Hz, 2H), 2.03 (s, 3H), 1.83 (ddd, *J* = 14.7, 7.8, 7.8 Hz, 1H), 1.60 (ddd, *J* = 14.2, 3.9, 3.9 Hz, 1H), 1.03 (s, 9H), 0.91 (s, 3H), 0.84 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$)

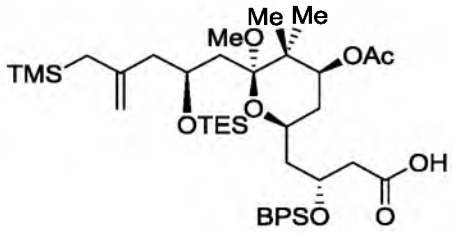
δ 201.3, 176.8, 170.6, 136.0, 135.9, 133.4, 130.1, 130.0, 127.9, 104.1, 72.8, 69.0, 66.6, 48.7, 48.8, 45.8, 43.4, 43.1, 42.0, 32.9, 27.0, 21.3, 20.8, 19.4, 17.5. 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 48.7, 27.0, 21.3, 20.8, 17.5; CH_2 δ 45.8, 43.4, 43.1, 32.9; CH δ 201.3, 136.0, 135.9, 130.1, 130.0, 127.9, 72.8, 69.0, 66.6; CH_0 δ 176.8, 170.7, 133.8, 133.4, 104.1, 42.0, 19.4; IR (neat) 2944, 2858, 1724, 1473, 1428, 1367, 1389, 1029 cm^{-1}; HRMS (ESI) calcd for C32H44O8NaSi (M+Na) 607.2703, found 607.2708.



(*R*)-4-((2*S*,4*S*,6*S*)-4-acetoxy-6-((*S*)-2-hydroxy-4-((trimethylsilyl)methyl)pent-4-en-1-yl)-6-methoxy-5,5-dimethyltetra hydro-2*H*-pyran-2-yl)-3-((*tert*-butyldiphenyl silyl)oxy)butanoic acid (2.67). A 5 ml rb flask, was charged with *N*,*N*'-((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfon amide) (147 mg, 0.282 mmol, 3.0 equiv) and heated to 90 °C under 0.2 mm Hg vacuum. After 18 h, the dry powder was cooled to rt, and the flask was flushed with Ar. CH_2Cl_2 (2 mL) was added via syringe and the suspension was cooled to 0 °C. Boron tribromide (27 μL, 0.282 mmol, 3.0 equiv) was added dropwise via syringe and the mixture was then stirred for 1 h at rt. The solvent was removed under high vacuum and the flask was purged with Ar. A mixture of trimethyl(2-((tributylstannyl)methyl) allyl)silane (118 mg, 0.282 mmol, 3.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (58 mg, 0.282 mmol, 3.0 equiv) in CH_2Cl_2 (1.5 mL + 0.5 mL rinse) was added via cannula. Stirring continued for 16 h under Ar.

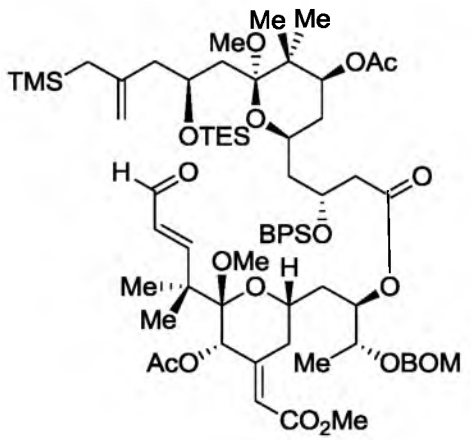
To a stirring solution of aldehyde **2.71** (55 mg, 0.094 mmol, 1.0 equiv) and CH_2Cl_2 (5 mL) at -78 °C in a 15 ml rb flask, was added the previously prepared solution of (4*S*,5*S*)-4,5- diphenyl-1,3-ditosyl-2-(2-((tri methyl silyl)methyl) allyl)-1,3,2-diazaborolidine dropwise via cannula. TLC analysis after 3 h at -78 °C indicated complete consumption of the aldehyde starting material. The mixture was quenched by the addition of pH 4 aqueous buffer (5 mL), then diluted with EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated by about 3/4 the volume under reduced pressure. Et_2O/ hexanes (15 mL of 2:1) was added, *N*,*N*'-((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) was recovered via filtration, and the solid was washed with copious amounts of 2:1 Et_2O/hexanes. The filtrate was concentrated under reduced pressure and purification was accomplished by flash column chromatography using a 1.0 × 10.0 cm silica gel column, eluting with 20% acetone/ hexanes, collecting 4 mL fractions. The product containing fractions (9-45) were combined and concentrated under reduced pressure to yield silane **2.67** (55 mg, 71%) as a colorless oil and as a 6:1 mixture of diastereomers as measured by NMR: $R_f = 0.42$ (5:4:1 hexanes: EtOAc: MeOH); $[\alpha]_D^{20} =$ +14.6 (c = 0.6, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.71-7.61 (m, 4H), 7.46-7.33 (m, 6H), 5.10 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.64 (s, 1H), 4.61 (s, 1H), 4.26 (dddd, *J* = 5.9, 5.9, 5.9, 5.9 1H), 4.08–4.02 (m, 1H), 3.64-3.56 (m, 1H), 2.94 (s, 3H), 2.57 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.54 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.20 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.03 (s, 3H), 1.92 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.88-1.83 (m, 1H), 1.79 (d, *J* = 3.9 Hz, 1H), 1.68-1.48 (m, 4H), 1.40-1.28 (m, 3H), 1.04 (s, 9H), 0.93 (s, 6H), 0.03 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 170.8, 144.2, 136.0, 135.9, 133.8, 130.0, 127.9, 127.8, 110.4, 104.8, 73.3, 68.3, 67.4,

66.3, 49.1, 48.0, 46.0, 44.0, 42.5, 42.1, 39.4, 33.0, 28.5, 28.0, 27.1, 27.0, 21.4, 20.4, 19.4, 17.6, 13.8, -1.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 49.0, 27.1, 21.4, 20.4, 17.6, 13.8, -1.2; CH_2 δ 110.4, 46.0, 44.0, 39.4, 33.0, 28.5, 28.0; CH δ 136.0, 135.9, 130.0, 127.9, 127.8, 73.3, 68.3, 67.4, 66.3; CH_0 δ 170.8, 144.2, 133.8, 104.8, 48.0, 42.5, 42.1, 19.4; IR (neat) 3071, 2905, 2855, 1739, 1633, 1432, 1420, 1252, 1106, 1112, 1071, 1034, 846, 711, 617 cm^{-1}; HRMS (ESI) calcd for $C_{39}H_{60}NaO_8Si_2$ (M+Na) 735.3724, found 735.3729.



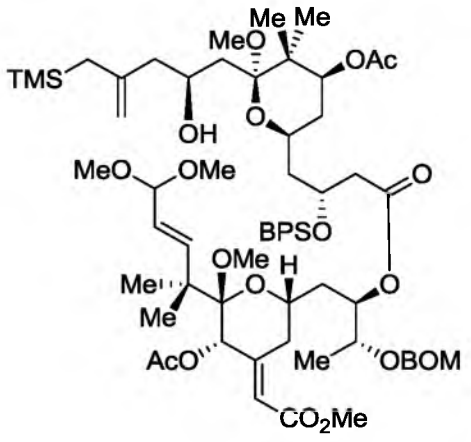
(*R*)-4-((2*S*,4*S*,6*S*)-4-acetoxy-6-methoxy-5,5-dimethyl-6-((*S*)-2-((triethylsilyl) oxy)-4-((trimethylsilyl)methyl)pent-4-en-1-yl)tetra hydro-2*H*-pyran-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy)butanoic acid (2.72).[38] To a stirring solution of alcohol **2.67** (40 mg, 0.056 mmol, 1.0 equiv), imidazole (19 mg, 0.280 mmol, 5.0 equiv), and CH_2Cl_2 (1 mL) in a 10 ml rb flask at 0 °C, was added TESCl (28 μL, 0.168 mmol, 3.0 equiv) dropwise via syringe. TLC analysis after 2 h indicated complete consumption of the alcohol starting material. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2.0 × 10.0 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 4 mL fractions. The product containing

fractions (14-45) were combined and concentrated under reduced pressure to yield TES ether **2.72** (44 mg, 95%) as clear oil: R_f = 0.56 (1:3:6 MeOH: EtOAc: hexanes); $[\alpha]_D^{20}$ = +19.1 (c = 0.6, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74–7.62 (m, 4H), 7.48–7.34 (m, 6H), 4.97 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.63 (s, 1H), 4.59 (s, 1H), 4.17–4.11 (m, 2H), 3.26 (dddd, *J* = 9.3, 6.4, 6.4, 2.9 1H), 2.95 (s, 3H), 2.68 (dd, *J* = 15.1, 3.9 Hz, 1H), 2.54 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.13 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.02 (s, 3H), 1.90–1.82 (m, 2H), 1.72 (dd, *J* = 16.1, 7.3 Hz, 1H), 1.56 (ddd, *J* = 13.7, 5.9, 3.4 Hz, 1H), 1.50 (d, *J* = 9.8 Hz, 1H), 1.30 (ddd, *J* = 12.2, 4.9, 2.9 Hz, 1H), 1.03 (s, 9H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.90 (s, 3H), 0.89 (s, 3H), 0.59 (q, *J* = 8.3 Hz, 6H), 0.03 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 176.1, 170.8, 144.4, 136.1, 136.0, 133.8, 133.3, 130.1, 130.0, 127.9, 127.9, 127.9, 110.8, 104.5, 74.1, 69.0, 68.4, 65.6, 48.6, 48.4, 43.4, 42.6, 42.0, 39.8, 32.7, 27.0, 21.4, 20.9, 19.4, 17.2, 7.3, 5.7, -1.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 48.6, 27.0, 21.4, 20.9, 17.4; CH_2 δ 110.8, 48.4, 43.4, 42.6, 39.8, 32.7, 5.7; CH δ 136.1, 136.0, 130.1, 130.0, 127.9, 74.1, 69.0, 68.4, 65.6; CH_0 δ 176.1, 170.8, 144.4, 133.8, 133.3, 104.5, 42.0, 19.4, 7.3, -1.2; IR (neat) 3078, 2955, 2887, 1743, 1718, 1622, 1472, 1395, 1364, 1250, 1106, 1081, 1023, 854, 740, 702 cm^{-1}; HRMS (ESI) calcd for $C_{45}H_{74}NaO_8Si_3$ (M+Na) 849.4589, found 849.4607.



(*R*)-(2*R*,3*R*)-1-((2*S*,5*S*,6*S*,*E*)-5-acetoxy-6-methoxy-4-(2-methoxy-2-oxoethyl idene)-6-((*E*)-2-methyl-5-oxopent-3-en-2-yl)tetrahydro-2*H*-pyran-2-yl)-3-((benzyloxy)methoxy)butan-2-yl 4-((2*S*,4*S*,6*S*)-4-acetoxy-6-methoxy-5,5-dimethyl-6-((*S*)-2-((triethylsilyl)oxy)-4-((trimethylsilyl) methyl)pent-4-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy) butanoate (2.79). To a stirring mixture of acid **2.72** (16 mg, 0.019 mmol, 1.2 equiv), Et_3N (16 μL, 0.116 mmol, 6.0 equiv), and toluene (2 mL) in a 10 mL round bottom flask at 0 °C, was added 2,4,6-trichlorobenzoyl chloride (9 μL, 0.059 mmol, 3.0 equiv) dropwise via syringe. The reaction was allowed to proceed for 4 h at rt, after which time TLC analysis indicated complete consumption of the acid starting material. To a stirring mixture of this anhydride at 0 °C, was added a solution of alcohol **2.68** (9 mg, 0.016 mmol, 1.0 equiv) and DMAP (7 mg, 0.058 mmol, 3.0 equiv) in toluene (0.5 mL) dropwise via cannula. An additional toluene (0.2 mL) was used twice to rinse the remaining the alcohol residue from the flask via cannula. The reaction was allowed to proceed for 1 h at rt, after which time TLC analysis indicated complete consumption of the alcohol starting material. Purification was accomplished by directly loading the suspension onto a 1.0 × 5.0 cm silica gel flash column, rinsing with toluene, then eluting with 10% EtOAc/hexanes, collecting 4 mL fractions. The product containing

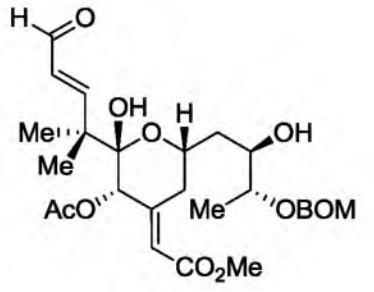
fractions (10-20) were combined and concentrated under reduced pressure to yield ester **2.73** (18 mg, 82%) as a white foam: R_f = 0.45 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.53 (d, *J* = 7.8 Hz, 1H), 7.74-7.64 (m, 5H), 7.45-7.28 (m, 11H), 5.96-5.88 (m, 2H), 5.37 (dd, *J* = 5.9, 2.0 Hz, 1H), 4.98 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.83 (s, 1H), 4.66 (s, 2H), 4.62 (s, 1H), 4.57 (s, 1H), 4.25-4.09 (m, 2H), 3.89 (dddd, *J* = 10.3, 6.4, 6.4 Hz, 1H), 3.89 (dd, *J* = 11.3, 11.3 Hz, 1H), 3.70 (s, 3H), 3.38-3.31 (m, 1H), 3.25 (s, 3H), 2.96 (s, 3H), 2.54-2.46 (m, 2H), 2.27(t, *J* = 11.7 Hz, 1H), 2.04 (s, 3H), 1.89 (s, 3H), 1.99-1.96 (m, 1H), 1.75-1.60 (m, 2H), 1.55-1.44 (m, 2H), 1.30-1.22 (m, 5H), 1.20 (s, 3H), 1.19 (s, 3H), 1.00 (s, 9H), 0.94 (t, *J* = 4.9 Hz, 9H), 0.90 (s, 3H), 0.86 (s, 3H), 0.58 (q, *J* = 7.8 Hz, 6H), 0.03 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.9, 170.7, 168.9, 167.1, 166.5, 137.9, 136.1, 136.0, 134.1, 133.6, 130.0, 129.9, 128.7, 128.0, 127.9, 127.8, 127.7, 126.8, 118.7, 110.8, 104.3, 102.6, 93.7, 74.1, 73.0, 71.8, 71.4, 69.8, 68.8, 68.7, 68.3, 65.3, 51.7, 51.5, 48.7, 48.4, 47.3, 43.5, 42.6, 42.0, 39.8, 35.8, 32.7, 32.1, 29.9, 27.5, 27.0, 24.1, 21.8, 21.5, 21.0, 20.2, 19.4, 17.2, 16.2, 7.3, 7.2, 5.7, -1.2.



(*R*)-(2*R*,3*R*)-1-((2*S*,5*S*,6*S*,*E*)-5-acetoxy-6-((*E*)-5,5-dimethoxy-2-methylpent-3-en-2-yl)-6-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2*H*-pyran-2-yl)-3-

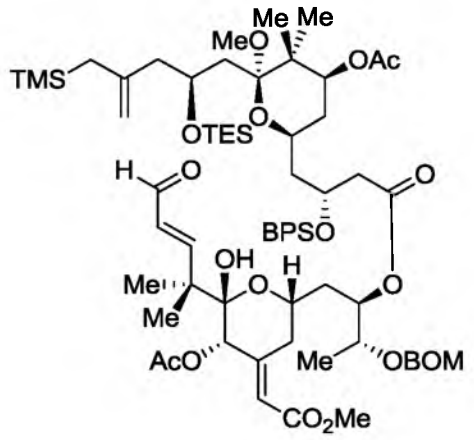
((benzyloxy)methoxy)butan-2-yl 4-((2*S*, 4*S*,6*S*)-4-acetoxy-6-((*S*)-2-hydroxy-4-((trimethylsilyl)methyl)pent-4-en-1-yl)-6-meth oxy-5,5-dimethyltetrahydro-2*H*-pyran-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy) butanoate (2.74). To aldehyde **2.73** (12 mg, 0.010 mmol, 1.0 equiv) in a 4 mL vial, was added a solution of PPTS (0.1 M in EtOH, 20 μL, 0.002 mmol, 0.2 equiv) via syringe and the vial was sealed with a Teflon cap. TLC analysis after 12 h indicated complete consumption of the aldehyde starting material. The solution was brought to dryness under a steady stream of N_2, dissolved in MeOH (1 mL), and stirred for 5 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL), then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 1.0 × 4.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (10-15) were combined and concentrated under reduced pressure to yield dimethyl acetal **2.74** (8 mg, 70%) as a clear oil: R_f = 0.53 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.66 (m, 5H), 7.46-7.28 (m, 10H), 6.18 (d, *J* = 16.1 Hz, 1H), 5.89 (s, 1H), 5.39-5.25 (m, 2H), 5.09 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.80 (s, 1H), 4.72-4.58 (m, 3H), 4.25 (ddd, *J* = 11.4, 5.8, 5.8 Hz, 1H), 4.08 (ddd, *J* = 12.5, 6.5. 6.5 Hz, 1H), 3.94-3.88 (m, 2H), 3.78 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.69 (s, 3H), 3.67-3.60 (m, 1H), 3.53-3.44 (m, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 3.00 (s, 3H), 2.60-2.40 (m, 3H), 2.28 (t, *J* = 13.7 Hz, 1H), 2.23-2.14 (m, 1H), 2.04 (s, 3H), 1.99-1.82 (m, 3H), 1.75-1.50 (m, 7H), 1.27 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.02 (s, 9H), 0.93 (s, 3H), 0.85 (s, 3H), 0.04 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 170.7, 170.7, 169.5,

166.7, 152.0, 144.5, 143.0, 138.0, 136.1, 136.0, 133.9, 133.6, 130.1, 128.6, 128.0, 127.9, 127.9, 121.6, 117.7, 110.3, 105.0, 104.3, 102.7, 93.7, 73.4, 73.3, 72.1, 71.9, 69.8, 68.3, 67.7, 67.3, 66.0, 64.2, 52.8, 51.5, 51.3, 51.4, 49.2, 46.3, 46.2, 43.8, 42.5, 42.1, 39.5, 36.2, 33.1, 32.5, 32.1, 29.9, 27.1, 24.7, 23.3, 22.9, 21.5, 21.3, 20.6, 20.5, 19.4, 17.6, 15.9, 14.3, -1.2.



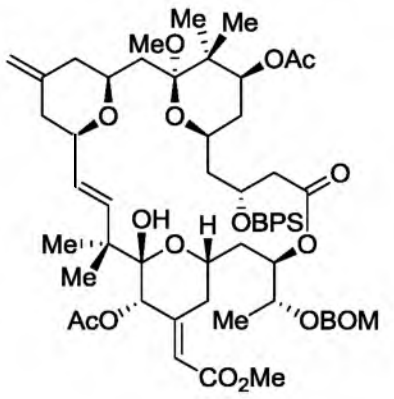
(*E*)-methyl 2-((2*S*,3*S*,6*S*)-3-acetoxy-6-((2*R*,3*R*) -3-((benzyloxy)methoxy)-2-hydroxybutyl)-2-hydroxy-2-((*E*)-2-methyl-5-oxopent -3-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-ylidene)acetate (2.77). To a stirring solution of PMB ether **2.25** (444 mg, 0.660 mmol, 1.0 equiv) and CH_2Cl_2/H_2O (99:1, 15 mL) at 0 ºC in a 50 ml rb flask, was added DDQ (225 mg, 0.990 mmol, 1.5 equiv). TLC analysis after 2 h at 0 ºC indicated complete consumption of the PMB ether starting material. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 3.0 × 14.0 cm silica gel column, eluting with 20% EtOAc/Hexanes (300 mL) and 30% EtOAc/Hexanes, collecting 8 mL fractions. The product containing fractions (30-60) were combined and concentrated under reduced pressure to yield the crude alcohol.

To a stirring solution of this crude product in CH_3CN (15 mL) at 0 °C in a 50 mL plastic bottle, was added HF (48% in H_2O, 2.2 mL) dropwise via plastic syringe. The reaction mixture was stirred for 2 h at rt. The reaction mixture was quenched by pipetting into a stirring mixture of saturated aqueous $NaHCO_3$ solution (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 3.0 × 12.0 cm silica gel column, eluting with 50% EtOAc/Hexanes, collecting 8 mL fractions. The product containing fractions (14-50) were combined and concentrated under reduced pressure to yield alcohol **2.77** (306 mg, 87%) as a foam: R_f = 0.46 (60% EtOAc/hexanes); $[\alpha]_D^{20}$ = -24.1 (c = 0.9, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.50 (d, *J* = 7.8 Hz, 1H), 7.32-7.21 (m, 5H), 5.95 (d, *J* = 2.0 Hz, 1H), 5.90 (dd, *J* = 16.1, 7.8 Hz, 1H), 5.05 (s, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 2.9 Hz, 1H), 4.25 (brs, 1H), 4.14 (dddd, *J* = 11.0, 11.0, 2.1, 2.1 Hz, 1H), 3.73 (ddd, *J* = 8.3, 3.9, 2.4 Hz, 1H), 3.63 (s, 3H), 3.60 (d, *J* = 2.0 Hz, 1H), 3.55 (dddd, *J* = 6.4, 6.4, 6.4, 6.4 Hz, 1H), 2.09-1.94 (m, 2H), 1.78 (s, 3H), 1.70 (ddd, *J* = 13.7, 10.8, 2.5 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 3H), 1.04 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.9, 169.0, 166.5, 166.4, 150.2, 137.5, 128.0, 127.6, 121.0, 99.9, 93.8, 77.6, 72.9, 71.0, 70.0, 67.0, 51.5, 46.6, 39.0, 31.3, 23.3, 21.5, 20.0, 16.8; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.5, 23.3, 21.5, 20.0, 16.5; CH_2 δ 93.8, 70.0, 39.0, 31.3; CH δ 194.6, 166.5, 128.7, 128.1, 128.0, 127.6, 121.0, 77.6, 72.9, 67.0; CH_0 δ 169.0, 166.4, 150.2, 137.5, 99.9, 46.6; IR (neat) 3466, 2978, 2947, 1750, 1724, 1689, 1440, 1378, 1212, 1165, 1095, 1037 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{38}O_{10}Na$ (M+Na) 557.2363, found 557.2371.



(*R*)-(2*R*,3*R*)-1-((2*S*,5*S*,6*S*,*E*)-5-acetoxy-6-hydroxy-4- (2-methoxy-2-oxoethyl idene)-6- ((*E*)-2-methyl-5-oxopent-3-en-2-yl) tetra hydro- 2*H*-pyran-2-yl)-3-((benzyloxy)methoxy)butan-2-yl 4-((2*S*,4*S*,6*S*)- 4-acetoxy-6-methoxy-5,5-dimethyl-6-((*S*)-2-((triethylsilyl)oxy)-4-((trimethylsilyl) methyl)pent-4-en-1-yl)tetrahydro- 2H-pyran-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy) butanoate (2.78). To a stirring mixture of acid **2.72** (73.2 mg, 0.080 mmol, 1.1 equiv), Et_3N (67 μL, 0.482 mmol, 6.0 equiv), and toluene (2 mL) in a 10 mL round bottom flask at 0 °C, was added 2,4,6-trichlorobenzoyl chloride (14 μL, 0.089 mmol, 1.1 equiv) dropwise via syringe. The reaction was allowed to proceed for 3h at rt, after which time TLC analysis indicated complete consumption of the acid starting material. To a stirring mixture of this anhydride at 0 °C, was added a solution of alcohol **2.77** (43.2 mg, 0.089 mmol, 1.0 equiv) and DMAP (29.0 mg, 0.241 mmol, 3.0 equiv) in toluene (0.5 mL) dropwise via cannula. An additional toluene (0.2 mL) was used twice to rinse the remaining alcohol residue from the flask via cannula. The reaction was allowed to proceed for 1 h at rt, after which time TLC analysis indicated complete consumption of the alcohol starting material. Purification was accomplished by directly loading the suspension onto a 3.0 × 12.0 cm silica gel flash column, rinsing with toluene, then eluting with 10% EtOAc/hexanes, collecting 4 mL fractions. The product

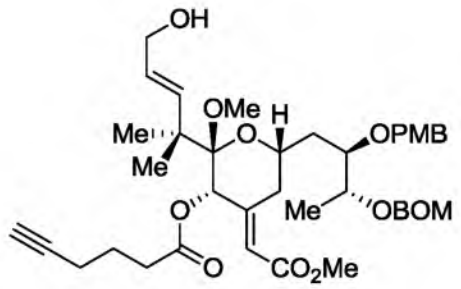
containing fractions (30-63) were combined and concentrated under reduced pressure to yield ester **2.78** (82 mg, 76%) as a white foam: R_f = 0.39 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +0.8 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.57 (d, *J* = 7.8 Hz, 1H), 7.74-7.62 (m, 5H), 7.45-7.28 (m, 11H), 6.00 (s, 1H), 5.97 (dd, *J* = 16.1, 7.8 Hz, 1H), 5.31-5.25 (m, 2H), 5.12 (s, 1H), 4.93 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.83 (d, *J* = 7.3 Hz, 1H), 4.79 (d, *J* = 7.3 Hz, 1H), 4.66 (s, 2H), 4.62 (brs, 1H), 4.57 (brs, 1H), 4.19-4.09 (m, 2H), 3.89 (dq, *J* = 5.9, 4.4 Hz, 1H), 3.85-3.80 (m, 1H), 3.69 (d, *J* = 1.5 Hz, 1H), 3.66 (s, 3H), 3.34-3.26 (m, 1H), 3.12 (s, 1H), 3.01-2.97 (m, 2H), 2.94(s, 3H), 2.57 (d, *J* = 5.9 Hz, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 1.99-1.96 (m, 1H), 1.88-1.86 (m, 2H), 1.56-1.44 (m, 2H), 1.30-1.22 (m, 5H), 1.19 (s, 3H), 1.16 (s, 3H), 0.99 (s, 9H), 0.93 (t, *J* = 4.9 Hz, 9H), 0.88 (s, 3H), 0.86 (s, 3H), 0.56 (q, *J* = 7.8 Hz, 6H), 0.03 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.9, 172.4, 170.8, 169.0, 166.6, 166.5, 150.3, 144.5, 138.0, 136.2, 136.0, 134.1, 133.6, 130.0, 129.9, 128.7, 128.6, 128.0, 127.9, 127.8, 127.6, 121.2, 110.3, 99.6, 93.5, 74.2, 73.8, 72.9, 72.8, 69.9, 68.4, 68.0, 66.4, 65.2, 52.1, 51.4, 48.7, 48.4, 46.0, 43.5, 42.4, 42.0, 39.8, 36.7, 32.5, 31.0, 29.9, 27.5, 27.0, 23.2, 21.6, 21.4, 20.9, 20.2, 19.4, 17.2, 16.4, 7.3, 7.2, 5.7, -1.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.4, 48.4, 27.0 ,23.2, 21.6, 21.4, 20.9, 20.2, 17.2, 17.2, 16.4, 7.3, -1.2; CH_2 δ 110.3, 93.5, 69.9, 68.0, 48.7, 43.5, 42.4, 39.8, 32.5, 31.0, 27.5, 5.7; CH δ 194.9, 166.6, 136.2, 136.0, 130.0, 129.9, 128.7, 128.6, 128.0, 127.9, 127.8, 127.6, 121.2, 74.2, 73.8, 72.9, 72.8, 68.4, 66.4, 65.2; CH_0 δ 172.4, 170.8, 169.0, 166.5, 150.3, 133.6, 99.6, 52.1, 46.0, 42.0, 36.7, 29.9, 19.4, 7.2; IR (neat) 3472, 2956, 2887, 1746, 1693, 1475, 1370. 1247, 1106, 1044, 880, 842, 706 cm^{-1}; HRMS (ESI) calcd for $C_{73}H_{110}NaO_{17}Si_3$ (M+Na) 1365.6949, found 1365.6974.



(3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*S*, 25*S*)-17-((*R*)-1-((benzyloxy)methoxy)ethyl)-21-((*tert*-butyldiphenylsilyl)oxy)-11-hydroxy-1-methoxy-13-(2-methoxy-2-oxoethylidene)-10,10,26,26-tetramethyl-5-methylene-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.1^{3,7}.1^{11,15}]nonacos-8-ene-12, 25-diyl diacetate (2.79). To aldehyde **2.78** (51 mg, 0.038 mmol, 1.0 equiv) in a 4 mL vial, was added a solution of PPTS (4 mM in EtOH, 1.9 mL, 0.008 mmol, 0.2 equiv) via syringe and the vial was sealed with a Teflon cap. TLC analysis after 14 h indicated complete consumption of the aldehyde starting material. The solution was brought to dryness under a steady stream of N_2, the residue was dissolved in MeOH (2 mL), and the resulting mixture was stirred for 5 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL), then diluted with CH_2Cl_2 (15 mL) and H_2O (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 1.0 × 8.0 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (15-45) were combined and concentrated under reduced pressure to yield bryopyran **2.79** (35 mg, 80%) as a white foam: R_f = 0.43 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ =

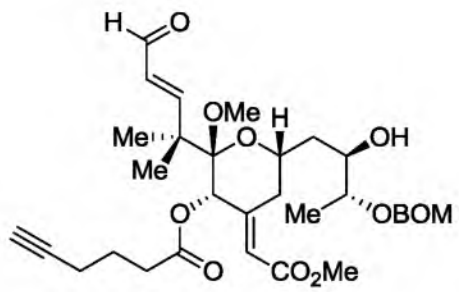
+21.2 (c = 1.0, $CHCl_3$); 500 MHz ^1H NMR ($CDCl_3$) δ 7.75-7.56 (m, 5H), 7.45-7.26 (m, 11H), 6.01 (d, *J* = 1.7 Hz, 1H), 5.97 (d, *J* = 16.1 Hz, 1H), 5.52 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.26-5.19 (m, 2H), 5.12 (s, 1H), 4.82 (s, 1H), 4.81 (s, 1H), 4.65-4.58 (m, 2H), 4.54 (d, *J* = 6.9 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 3.99 (ddd, *J* = 10.4, 7.5, 1.7 Hz, 1H), 3.90 (ddd, *J* = 11.3, 8.1, 1.8 Hz, 1H), 3.71 (s, 3H), 3.65-3.59 (m, 2H), 3.54 (ddd, *J* = 10.6, 8.4, 1.4 Hz, 1H), 2.73 (s, 3H), 2.65 (dd, *J* = 17.4, 3.4 Hz, 1H), 2.61 (s, 3H), 2.25 (dd, *J* = 17.5, 9.9 Hz, 1H), 2.18-2.09 (m, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03-1.92 (m, 2H), 1.71 (dd, *J* = 7.8, 5.0 Hz, 2H), 1.67-1.59 (m, 2H), 1.56-1.50 (m, 2H), 1.44 (dd, *J* = 13.6, 10.3 Hz, 1H), 1.32-1.24 (m, 2H), 1.18 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 9H), 1.00 (s, 3H), 0.94 (s, 6H), 0.83 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.0, 170.2, 169.4, 167.0, 151.2, 145.0, 138.0, 136.0, 135.8, 135.0, 135.3, 135.0, 134.3, 134.3, 134.2, 129.9, 129.8, 128.7, 128.1, 128.0, 127.9, 127.8, 120.2, 108.9, 103.0, 97.9, 93.8, 78.4, 74.4, 74.3, 73.1, 71.6, 69.7, 67.3, 65.0, 64.5, 51.4, 48.1, 45.4, 45.1, 42.7, 41.8, 41.5, 40.7, 39.8, 36.6, 33.7, 31.3, 29.9, 27.2, 24.3, 21.6, 21.5, 20.5, 20.1, 19.5, 17.5, 16.7, 14.3; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.4, 48.1, 27.2, 24.3, 21.6, 21.5, 20.5, 20.1, 16.7; CH_2 δ 108.9, 130.0, 93.8, 69.7, 45.4, 42.7, 41.5, 40.7, 39.8, 36.6, 33.7, 31.3, 29.9; CH δ 136.0, 135.8, 135.3, 134.3, 134.2, 129.9, 129.8, 128.7, 128.1, 128.0, 127.9, 127.8, 120.2, 78.4, 74.4, 74.3, 74.3, 73.1, 71.6, 67.3, 65.0, 64.5; CH_0 δ 171.0, 170.2, 169.4, 167.0, 151.2, 145.0, 138.0, 135.0, 134.3, 129.8, 97.9, 45.1, 41.8, 19.5, 14.3; IR (neat) 3500, 3134, 3070, 2954, 2858, 1759, 1672, 1587, 1513, 1463, 1442, 1240, 1177, 1046, 946, 822, 778, 706 cm^{-1}; HRMS (ESI) calcd for $C_{64}H_{86}NaO_{16}Si$ (M+Na) 1161.5583, found 1161.5577.

Experimental Procedures and Analytical Data for Merle 45



(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy) butyl)-2-((*E*)-5-hydroxy-2-methyl pent-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2*H*-pyran-3-yl hex-5-ynoate (2.81). To a stirring solution of the TBS ether **2.49** (100 mg, 0.119 mmol, 1.0 equiv) in THF (3 mL) at rt in a plastic bottle, was added HF•py (20% in pyridine, 0.6 mL). TLC analysis after 6 h at rt indicated complete consumption of the TBS ether starting material. The mixture was quenched by pipetting into a stirring mixture of saturated aqueous $NaHCO_3$ solution (30 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2 × 17 cm silica gel column, eluting with 40% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (15-24) were combined and concentrated under reduced pressure to yield alcohol **2.81** (80 mg, 93%) as a white foam: R_f = 0.30 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = -3.1 (c = 1.1, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.18 (m, 7H), 6.86-6.82 (m, 2H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.89 (s, 1H), 5.38 (dt, *J* = 16.0, 6.3 Hz, 1H), 5.45 (s, 1H), 4.86 (d, *J* = 3.0 Hz, 2H), 4.68 (s, 2H), 4.62 (d, *J* = 9.0 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H),), 4.15 (dddd, *J* = 11.1, 6.3, 6.3, 6.3 Hz, 1H), 4.10-4.01 (m, 2H), 3.91 (ddd, *J* = 9.6, 4.2, 1.5 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.47 (dd, *J* = 15.9, 2.1 Hz, 1H),

3.23 (s, 3H), 2.46 (t, J = 7.8 Hz, 2H), 2.38-2.30 (m, 1H), 2.27 (dd, J = 6.5, 2.6 Hz, 1H), 2.00 (dd, J = 2.6, 2.6 Hz, 1H), 1.93 (ddd, J = 14.2, 10.0, 1.5 Hz, 1H), 1.87-1.80 (m, 2H), 1.74 (ddd, J = 12.7, 9.8, 1.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 3H), 1.13 (s, 3H), 1.10 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.7, 166.8, 159.4, 152.4, 139.7, 138.0, 130.6, 129.8, 129.5, 128.7, 128.0, 127.9, 125.1, 117.5, 114.0, 102.7, 93.5, 83.2, 76.7, 72.3, 71.9, 69.6, 68.6, 64.3, 55.4, 51.5, 46.2, 36.3, 33.2, 29.9, 24.2, 24.1, 23.3, 17.9; DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 51.5, 24.2, 24.1; CH_2 δ 93.5, 71.9, 69.6, 64.3, 36.3, 33.2, 29.9, 23.3, 17.9; CH δ 139.7, 129.8, 129.5, 128.7, 128.0, 127.9, 125.1, 117.7, 114.0, 83.2, 76.7, 72.3, 69.7; CH_0 δ 171.7, 166.8, 159.4, 152.4, 138.0, 130.6, 102.7, 68.7, 46.2; IR (neat) 3496, 3292, 2935, 1740, 1719, 1664, 1612, 1514, 1455, 1436, 1382, 1248, 1153, 1105, 1040, 821, 750 cm^{-1}; HRMS (ESI) calcd for $C_{41}H_{54}NaO_{11}$ (M+Na) 745.3564, found 745.3544.

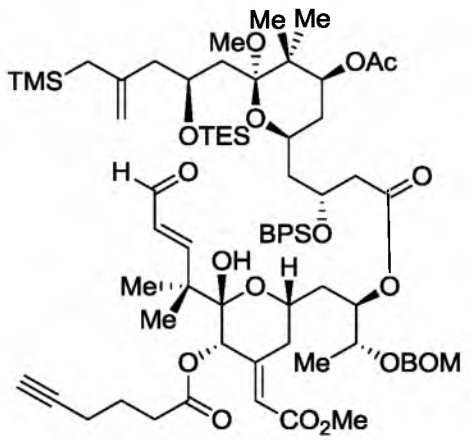


(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-hydroxybutyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-5-oxopent-3-en-2-yl)tetrahydro-2*H*-pyran-3-yl hex-5-ynoate (2.82). To a stirring solution of the allylic alcohol **2.81** (77 mg, 0.106 mmol, 1.0 equiv) in benzene (2 mL) at rt in a 10 ml rb flask, was added activated MnO_2 (267 mg, 3.1 mmol, 30.0 equiv). TLC analysis after 3 h indicated complete consumption of the allylic alcohol starting material. The reaction mixture was filtered over a pad (5.0 × 0.5 cm) of Celite®, washing with copious amounts of Et_2O, and concentrated

under reduced pressure to give the crude aldehyde that was taken directly onto the next reaction without further purification.

To a stirring solution of the crude aldehyde in H_2O (100 μL) and CH_2Cl_2 (2 mL) at 0 °C in a 10 ml rb flask, was added DDQ (47 mg, 0.206 mmol, 1.9 equiv). The reaction mixture was stirred for 4 h at 0 °C. The reaction mixture was quenched by transfer into a 25 mL separatory funnel that contained a mixture of a saturated $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 2 × 14 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (51-69) were combined and concentrated under reduced pressure to yield alcohol **2.82** (49 mg, 77%) as a white foam: R_f = 0.46 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = -15.0 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.50 (d, *J* = 7.6 Hz, 1H), 7.34-7.19 (m, 6H), 5.88 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.83 (s, 1H), 5.40 (s, 1H), 4.60 (ABq, *J* = 11.7 Hz, Δν = 24.2 Hz, 2H), 4.23-7.15 (m, 1H), 3.82-3.75 (m, 1H), 3.63 (s, 3H), 3.58 (ddd, *J* = 12.4, 6.2, 6.2 Hz, 1H), 3.45 (dd, *J* = 15.6, 1.5 Hz, 1H), 3.37 (s, 3H), 2.68 (s, 1H), 2.36-2.11 (m, 5H), 1.93 (dd, *J* = 2.8, 2.8 Hz, 1H), 1.76-1.61 (m, 4H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.13 (s, 3H), 1.10 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.8, 171.2, 167.1, 166.5, 151.6, 137.5, 128.7, 128.0, 126.9, 117.9, 102.5, 94.0, 82.9, 78.3, 77.3, 71.7, 71.1, 70.1, 69.9, 68.6, 51.7, 51.5, 47.6, 39.8, 33.0, 32.9, 24.1, 23.2, 22.0, 17.8, 17.0; DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.7, 51.5, 24.1, 22.0, 17.0; CH_2 δ 94.0, 70.1, 39.8, 33.0, 32.9, 23.2, 17.8; CH δ 194.8, 167.1, 128.7, 128.0, 126.9, 117.9, 78.2, 71.7, 71.1, 69.9, 68.6; CH_0 δ 171.7, 166.8, 159.4, 152.4, 138.0, 130.6, 102.7, 68.7, 46.2; IR (neat) 3543, 3292, 2948, 1738, 1715, 1682, 1633, 1471, 1435, 1385, 1338,

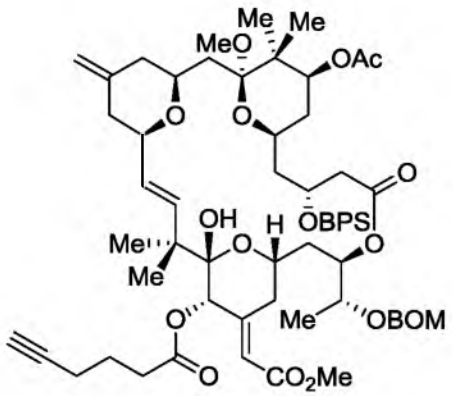
1038, 937, 744, 698 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{44}NaO_{10}$ (M+Na) 623.2832, found 623.2851.



(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-2-(((*R*)-4-((2*S*,4*S*,6*S*) -4-acetoxy- 6-methoxy -5,5-dimethyl -6-((*S*)-2- ((triethylsilyl)oxy)-4-((tri methylsilyl)methyl)pent-4-en-1-yl) tetrahydro-2*H*-pyran-2-yl)-3- ((*tert*-butyldiphenyl silyl)oxy)butanoyl) oxy)-3-((benzyloxy) methoxy) butyl)-2-hydroxy -4-(2-methoxy-2-oxoethylidene)-2-((*E*)- 2-methyl-5-oxopent-3-en-2-yl)tetrahydro-2*H*- pyran-3-yl hex-5-ynoate (2.83). To a stirring solution of methyl ketal **2.82** (35 mg, 0.058 mmol, 1.0 equiv) in CH_3CN/H_2O (4:1, 1.5 mL) at 0 ºC in a 5 mL plastic bottle, was added HF (48% in H_2O, 150 µL) dropwise via plastic syringe. TLC analysis after 6 h at rt indicated complete consumption of the ketal starting material. The reaction mixture was quenched by pipetting into a stirring mixture of saturated aqueous $NaHCO_3$ solution (10 mL) and EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude hemiketal that was taken directly onto the next reaction without further purification.

Separately, to a stirring solution of acid **2.72** (51 mg, 0.062 mmol, 1.1 equiv), Et_3N (40 μL, 0.280 mmol, 5.0 equiv), and toluene (1 mL) in a 10 mL round bottom flask at 0 °C, was added 2,4,6-trichlorobenzoyl chloride (10 μL, 0.062 mmol, 1.0 equiv) via syringe. The reaction was allowed to proceed for 4 h at rt, after which time TLC analysis indicated complete consumption of the acid starting material. To this stirring mixture of anhydride at 0 °C, was added a solution of crude alcohol and DMAP (7 mg, 0.058 mmol, 3.0 equiv) in toluene (0.5 mL) dropwise via cannula. Additional toluene (0.2 mL) was used twice to rinse the remaining alcohol residue from the flask via cannula. The reaction was allowed to proceed for 1 h at rt. Purification was accomplished by directly loading the suspension onto a 2 × 12 cm silica gel flash column, rinsing with toluene, then eluting with 20% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (60-78) were combined and concentrated under reduced pressure to yield ester **2.83** (55 mg, 70%) as a white foam: R_f = 0.32 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -6.2 (c = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.57 (d, *J* = 7.9 Hz, 1H), 7.71-7.64 (m, 5H), 7.45-7.28 (m, 11H), 6.00 (s, 1H), 5.98 (dd, *J* = 16.5, 8.1 Hz, 1H), 5.28 (ddd, *J* = 9.2, 3.9, 2.2 Hz, 1H), 5.14 (s, 1H), 4.93 (dd, *J* = 11.8, 4.8 Hz, 1H), 4.82 (ABq, *J* = 7.0 Hz, Δν = 21.7 Hz, 2H), 4.65 (s, 2H), 4.61 (s, 1H), 4.57 (s, 1H), 4.20-4.08 (m, 2H), 3.92-3.86 (m, 1H), 3.86-3.78 (m, 1H), 3.35-3.26 (m, 1H), 3.19 (s, 1H), 3.00-2.95 (m, 2H), 2.93 (s, 3H), 2.58 (d, *J* = 5.5 Hz, 2H), 2.32-2.23 (m, 1H), 2.21-2.16 (m, 2H), 2.12-2.04 (m, 1H), 2.02 (s, 3H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.94-1.66 (m, 5H), 1.57-1.45 (m, 2H), 1.30-1.25 (m, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 0.98 (s, 9H), 0.93 (t, *J* = 5.0 Hz, 9H), 0.88 (s, 3H), 0.86 (s, 3H), 0.64-0.54 (m, 6H), 0.04 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.8, 172.4, 171.2, 170.8, 166.5, 150.2, 137.8, 136.0, 134.1, 133.5, 130.0, 129.9, 128.7, 128.0, 127.9, 127.8, 127.7, 121.2, 110.8,

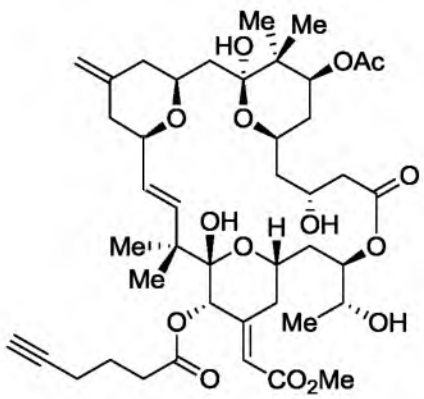
104.3, 99.7, 93.5, 83.0, 74.2, 73.7, 73.0, 72.8, 69.8, 68.4, 68.0, 66.4, 65.2, 51.4, 48.7, 48.4, 45.9, 43.5, 42.4, 42.0, 39.8, 36.7, 33.2, 31.1, 29.9, 27.5, 27.0, 23.2, 23.1, 21.4, 20.9, 20.3, 19.4, 17.8, 17.2, 16.3, 7.3, 5.6, -1.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.4, 48.4, 27.0, 23.2, 21.4, 20.9, 20.3, 17.2, 16.3, 7.3, -1.2; CH_2 δ 110.8, 93.5, 69.8, 48.7, 43.5, 42.4, 39.8, 36.7, 33.2, 31.1, 29.9, 27.5, 23.2, 17.8, 5.6; CH δ 194.8, 166.5, 136.2, 136.0, 130.0, 129.9, 128.7, 128.0, 127.9, 127.8, 121.2, 74.2, 73.7, 73.0, 72.8, 69.8, 68.4, 68.0, 66.4, 65.2; CH_0 δ 172.4, 171.2, 170.8, 150.2, 144.5, 137.8, 134.1, 133.5, 104.2, 99.7, 83.0, 45.9, 42.0, 25.1, 19.4; IR (neat) 3479, 3306, 2951, 2733, 1738, 1732, 1688, 1633, 1471, 1455, 1385, 1246, 1042, 855, 739, 702, 613 cm^{-1}; HRMS (ESI) calcd for $C_{73}H_{110}NaO_{17}Si_3$ (M+Na) 1417.7262, found 1417.7255.



(3*S*,7*R*,8*E*,11*S*,12*S*, 13*E*,15*S*,17*R*, 21*R*,23*S*,25*S*)-25 -acetoxy- 17-((*R*) -1-((benzyloxy)methoxy)ethyl) -21-((*tert*-butyl diphenylsilyl)oxy) -11-hydroxy -1-methoxy-13-(2-methoxy-2-oxoethylidene)-10,10,26 ,26-tetramethyl-5-methylene-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.1^{3,7}.^{111,15}] nonacos-8-en-12-yl hex-5-ynoate (2.80). To aldehyde **2.83** (25 mg, 0.018 mmol, 1.0 equiv) in EtOH (1 mL) in a 4 mL vial, was added PPTS (1.8 mg, 0.007 mmol, 0.4 equiv). TLC analysis after stirring for 16 h

indicated complete consumption of the aldehyde starting material. The solution was brought to dryness under a steady stream of N_2, dissolved in MeOH (1 mL), and stirred for 5 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL), then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 1 × 10 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (7-26) were combined and concentrated under reduced pressure to yield bryopyran **2.80** (14.6 mg, 70%) as a white foam: R_f = 0.34 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +8.1 (c = 0.5, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69-7.57 (m, 5H), 7.41-7.29 (m, 11H), 6.01 (d, *J* = 2.1 Hz, 1H), 5.97 (s, 1H), 5.52 (dd, *J* = 16.3, 7.6 Hz, 1H), 5.26-5.19 (m, 2H), 5.14 (s, 1H), 4.96-4.93 (m, 1H), 4.84-4.80 (m, 1H), 4.65-4.58 (m, 1H), 4.53 (ABq, *J* = 7.0 Hz, Δν = 25.6 Hz, 2H), 4.49 (ABq, *J* = 7.0 Hz, Δν = 18.9 Hz, 2H), 3.99 (ddd, *J* = 10.8, 7.4, 1.5 Hz, 1H), 3.93-3.87 (m, 1H), 3.71 (s, 3H), 3.65-3.59 (m, 2H), 3.57-3.51 (m, 1H), 2.73 (s, 3H), 2.66 (dd, *J* = 17.6, 3.5 Hz, 1H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.26 (dd, *J* = 7.1, 2.9 Hz, 1H), 2.24 (dd, *J* = 6.9, 2.6 Hz, 1H), 2.16-2.09 (m, 2H), 2.05 (s, 3H), 2.02-1.95 (m, 3H), 1.92-1.81 (m, 3H), 1.75-1.60 (m, 3H), 1.57-1.51 (m, 2H), 1.45 (dd, *J* = 13.5, 10.2 Hz, 1H), 1.32-1.24 (m, 1H), 1.18 (s, 3H), 1.06 (d, *J* = 6.3 Hz, 3H), 1.02 (s, 9H), 0.94 (s, 6H), 0.83 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.6, 171.1, 170.3, 167.0, 151.2, 144.9, 137.9, 135.9, 135.8, 135.4, 135.0, 134.3, 134.0, 129.9, 129.8, 128.7, 128.1, 128.0, 127.9, 127.8, 120.3, 109.0, 103.0, 98.0, 93.8, 83.2, 78.5, 74.5, 74.4, 73.1, 71.6, 69.7, 69.6, 67.2, 65.0, 64.5, 51.5, 48.2, 45.4, 45.1, 42.7, 41.8, 41.4, 40.7, 39.9, 36.6, 33.3, 31.3, 29.9, 27.0,

24.4, 23.4, 21.6, 20.5, 20.0, 19.6, 17.9, 16.7; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.5, 48.2, 27.0, 24.2, 21.6, 20.0, 17.5, 16.7; CH_2 δ 109.0, 93.8, 69.7, 45.4, 42.7, 41.4, 40.7, 39.9, 36.6, 33.3, 31.3, 29.9, 23.4, 17.9; CH δ 135.9, 135.8, 135.4, 134.0, 129.9, 129.8, 128.7, 128.1, 128.0, 127.9, 127.8, 120.3, 78.5, 77.4, 74.5, 74.4, 73.1, 71.6, 67.2, 65.0, 64.5; CH_0 δ 171.6, 171.1, 170.3, 167.0, 151.2, 144.9, 137.9, 135.0, 134.3, 103.0, 98.0, 83.2, 45.1, 41.8, 19.6; IR (neat) 3508, 3309, 2930, 1738, 1667, 1633, 1471, 1455, 1385, 1246, 1154, 1111, 852, 742, 702, 622 cm^{-1}; HRMS (ESI) calcd for $C_{68}H_{90}NaO_{16}Si$ (M+Na) 1213.5896, found 1213.5896.

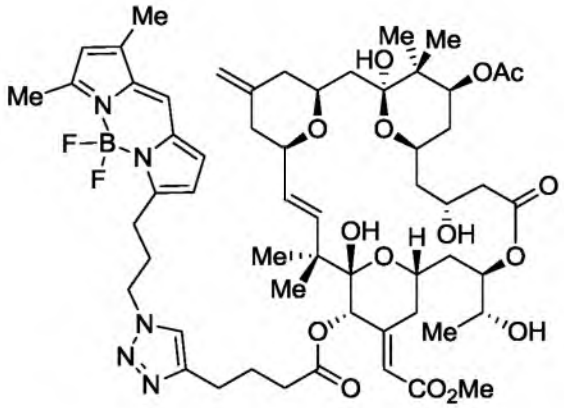


(3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R* ,23*R*,25*S*) -25-acetoxy -1,11,21-trihydroxy-17 -((*R*)-1-hydroxyethyl) -13-(2-methoxy-2-oxoethylidene) -10,10,26,26-tetramethyl-5- methylene-19-oxo-18,27,28,29-tetraoxa tetracyclo[21.3.1.$1^{3,7}$.$1^{11,15}$] nonacos-8-en-12-yl hex-5-ynoate (2.84). To a stirring solution of the BPS ether **2.80** (6.9 mg, 0.0058 mmol, 1.0 equiv) in THF (0.5 mL) in a 4 mL plastic bottle, was added HF•py (20 % in pyridine, 0.1 mL). TLC analysis after 85 h at rt indicated complete consumption of the BPS ether starting material. The mixture was quenched by pipetting into a stirring mixture of saturated aqueous $NaHCO_3$ solution (5 mL) and EtOAc (5 mL). The layers

were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude alcohol that was taken directly onto the next reaction without further purification.

To a stirring solution of the crude BOM ether in CH_3CN/ H_2O (25:1, 1 mL) in a 4 mL vial, was added $LiBF_4$ (22 mg, 0.232 mmol, 40.0 equiv). TLC analysis after stirring at 80 °C for 18 h indicated complete consumption of the starting material. The reaction mixture was cooled to rt, quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 0.5 × 4 cm silica gel column, eluting with 60% EtOAc/hexanes, collecting 1 mL fractions. The product containing fractions (7-12) were combined and concentrated under reduced pressure to yield bryopyran **2.84** (3.1 mg, 66%) as a clear film: R_f = 0.30 (60% EtOAc/hexanes); $[\alpha]_D^{20}$ = +1.1 (c = 0.8, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 1H), 5.31 (dd, *J* = 15.6, 8.5 Hz, 1H), 5.27 (s, 1H), 5.21 (ddd, *J* = 12.0, 5.5, 2.8 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.9 Hz, 1H), 5.14 (s, 1H), 4.76 (d, *J* = 7.4 Hz, 1H), 4.31-4.23 (m, 1H), 4.22-4.14 (m, 1H), 4.03 (tt, *J* = 11.0, 1.8 Hz, 1H), 3.85-3.79 (m, 1H), 3.73-3.70 (m, 1H), 3.68 (s, 3H), 3.67-3.62 (m, 1H), 3.45 (dd, *J* = 14.7, 7.4 Hz, 1H), 2.51-2.41 (m, 2H), 2.27 (dd, *J* = 6.9, 2.1 Hz, 1H), 2.25 (dd, *J* = 6.9, 2.4 Hz, 1H), 2.16-1.89 (m, 17H), 1.87-1.72 (m, 6H), 1.23 (d, *J* = 7.5 Hz, 3H), 1.16 (s, 3H), 1.00 (s, 6H), 0.95 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.5, 171.6, 171.0, 167.2, 151.8, 143.6, 138.8, 130.1, 120.0, 109.2, 102.1, 99.1, 83.2, 80.3, 77.4, 74.9, 73.9, 73.0, 72.2, 70.4, 69.6, 68.7,

66.0, 64.9, 51.3, 45.0, 42.8, 42.7, 42.2, 40.1, 36.0, 33.4, 31.4, 29.9, 24.9, 23.5, 21.4, 21.2, 20.0, 18.0, 17.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.3, 24.9, 21.4, 21.2, 20.0, 17.0; CH_2 δ 109.2, 42.8, 42.2, 40.1, 36.0, 33.6, 33.4, 31.4, 29.9, 23.5, 18.0; CH δ 138.8, 130.1, 120.0, 80.3, 77.4, 74.9, 73.9, 73.0, 72.2, 70.4, 69.6, 66.0, 64.9; CH_0 δ 171.6, 172.5, 171.6, 171.0, 167.2, 151.8, 143.6, 102.1, 99.1, 83.2, 68.7, 45.0,; IR (neat) 3466, 330, 2919, 2852, 2335, 1738, 1715, 1682, 1668, 1634, 1557, 1520, 1455, 1372, 1260, 1096, 802, 757, 667 cm^{-1}; HRMS (ESI) calcd for $C_{43}H_{62}NaO_{15}$ (M+Na) 841.3986, found 841.3997.



7-(3-(4-(4-(((3*S*,7*R*,8*E*,11*S*, 12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*) -25-acetoxy-1,11,21- trihydroxy- 17-((*R*)-1-hydroxy ethyl)-13-(2-methoxy-2-oxoethylidene)-10,10,26,26-tetramethyl-5-methylene-19-oxo-18,27,28,29-tetraoxatetracyclo [21.3.1.1^{3,7}.1^{11,15}]nonacos-8-en-12-yl)oxy)-4-oxobutyl)-1*H*-1,2,3-triazol-1-yl)propyl) -5,5- difluoro- 1,3-dimethyl- 5*H*- dipyrrolo[1,2-*c*:2',1'-*f*] [1,3,2]diazaborinin-4-ium-5-uide (Merle 45). To a stirring solution of alkyne **2.84** (1.8 mg, 0.0022 mmol, 1.0 equiv) and THF (0.6 mL) in a 4 mL reaction vial, was added freshly distilled (*i*Pr)$_2$NEt (2 μL, 0.011 mmol, 5.0 equiv) and copper(I) iodide (2.1 mg, 0.011 mmol, 5.0 equiv). Azide **2.47** (1.8 mg, 0.0066 mmol, 3.0 equiv) was added to the suspension, the reaction vial, was

sealed, and the mixture was allowed to stir at 70 °C for 18 h. The reaction suspension was cooled to rt, filtered over a pad (4.0 × 0.5 cm) of Celite®, washed with copious amounts of Et_2O, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using a 0.5 × 4 cm silica gel column, eluting with 1% MeOH/CH_2Cl_2, collecting 1 mL fractions. The product containing fractions (6-11) were combined and concentrated under reduced pressure to yield Merle 45 (2.0 mg, 80%) as a white foam: R_f = 0.37 (5% MeOH/ CH_2Cl_2); $[\alpha]_D^{20}$ = +4 (c = 0.05, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.10 (s, 1H), 6.89 (d, *J* = 3.7 Hz, 1H), 6.26 (d, *J* = 3.7 Hz, 1H), 6.14 (s, 1H), 5.98 (s, 1H), 5.77 (d, *J* = 15.8 Hz, 1H), 5.30 (dd, *J* = 15.8, 8.5 Hz, 1H), 5.24 (s, 1H), 5.20 (ddd, *J* = 11.5, 5.3, 2.5 Hz, 1H), 5.16 (dd, *J* = 11.7, 4.6 Hz, 1H), 5.13 (s, 1H), 4.75 (d, *J* = 8.0 Hz, 1H), 4.40 (d, *J* = 7.4 Hz, 1H), 4.29-4.13 (m, 2H), 4.05-3.98 (m, 1H), 3.84-3.76 (m, 1H), 3.71-3.68 (m, 1H), 3.67 (s, 3H), 3.66-3.60 (m, 1H), 3.48 (dd, *J* = 13.7, 6.7 Hz, 1H), 3.03 (d, *J* = 7.1 Hz, 1H), 3.01 (d, *J* = 7.5 Hz, 1H), 2.77-2.70 (m, 2H), 2.57 (s, 3H), 2.52-2.32 (m, 9H), 2.26 (s, 3H), 2.13-1.88 (m, 17H), 1.86-1.73 (m, 1H), 1.23 (d, *J* = 3.3 Hz, 3H), 1.12 (s, 3H), 1.00 (s, 6H), 0.96 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.5, 171.9, 171.0, 167.2, 160.7, 157.0, 151.9, 147.1, 144.3, 143.6, 138.8, 135.4, 130.0, 128.4, 124.0, 121.3, 119.9, 116.9, 109.2, 102.1, 99.1, 80.2, 74.5, 73.9, 73.0, 72.2, 70.4, 68.7, 66.1, 65.9, 64.9, 51.3, 49.9, 45.0, 42.6, 42.1, 34.1, 33.6, 32.1, 30.1, 29.9, 25.0, 24.9, 24.6, 22.9, 21.4, 20.0, 17.0, 15.5, 15.2, 11.6; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.3, 24.9, 21.4, 20.0, 17.0, 15.5, 15.2, 11.6; CH_2 δ 109.2, 66.1, 49.9, 42.6, 42.1, 41.3, 40.1, 34.1, 33.6, 32.1, 30.1, 29.9, 25.9, 24.6, 22.9; CH δ 138.8, 130.0, 128.4, 124.0, 121.3, 120.7, 119.9, 116.9, 80.2, 74.5, 73.9, 73.0, 72.2, 70.4, 68.7, 65.9, 64.9; CH_0 δ 172.5 171.9, 171.0, 167.2, 160.7, 157.0, 151.9, 147.1, 144.3, 143.6, 135.4, 130.0, 128.4, 102.1, 99.1,

45.0,; IR (neat) 3362, 2919, 2851, 1738, 1715, 1667, 1633, 1537, 1454, 1372, 1258, 1088, 798 cm^{-1}; HRMS (ESI) calcd for $C_{57}H_{78}BF_2N_5NaO_{15}$ (M+Na) 1144.5453, found 1144.5479.

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CHAPTER 3

THE SYNTHESIS OF THE CHROMENO[3,4-*b*]PYRROLE CORE.

Introduction

Fused pyrrolidine and chromene derivatives are common structural motifs of many natural products.[1] The chromenopyrrole core does not appear in any natural products to date, but has potential therapeutic use as a dopamine receptor antagonist. The 3,4-fused chromenopyrrole core has 3 different constitutional isomers as shown in Figure **3.1A**, where the nitrogen atom is placed at different positions in the pyrrole ring. The synthesis and biological effects of each isomer have been studied. Examples of biologically significant compounds containing the chromenopyrrole core are shown in Figure **3.1B**. Methoctramin, a chromeno[4,3-*b*]pyrrole, is an antagonist of the muscarinic acetylcholine receptor (mAChR)[2] and has shown selectivity for the M2 mAChR subtypes of the muscarinic receptors. Fiduxosin is an α1a-adrenoreceptor antagonist, which is selective for this specific isozyme and is being developed for the treatment of benign prostatic hyperplasia (BPH).[3] This drug contains a chromeno[3,4-*c*]pyrrole as part of its structure. Approaches to construct the 3,4-fused chromenopyrrole core are evaluated in the following sections.

A common way to construct chromeno[4,3-*b*]pyrrole ring systems is a [3 + 2] cycloaddition. An example of this methodology starts with the condensation of aldehyde **3.1** with 2-(methylamino)acetic acid and after sonication, an azomethine ylide reacts with the olefin to produce the tricyclic core **3.2**.[4] This reaction works beautifully with a variety

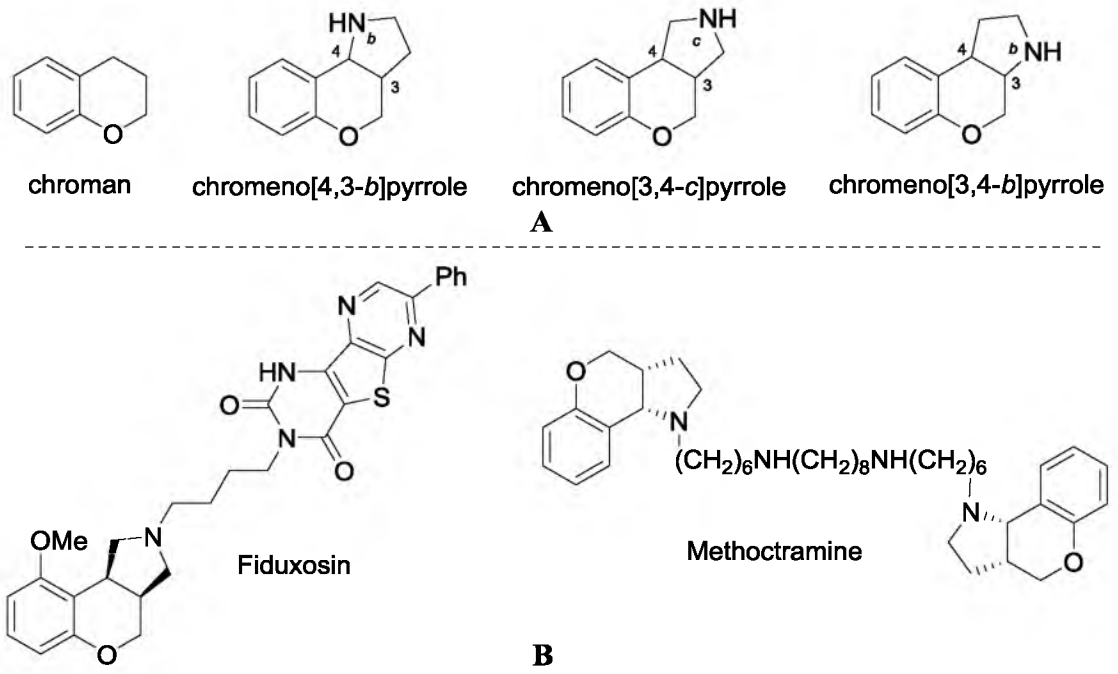


Figure 3.1. Constitutional Isomers of Chromenopyrroles (A) and Biologically Significant Chromenopyrroles (B)

of similar substrates. The Snider group also applied a similar 1,3-dipolar cycloaddition reaction (Figure **3.2**) to the construction of this core that was used as a model for the pyrroloquinoline core during their studies toward the total synthesis of martinellic acid.[5] This reaction works well giving exclusively the *cis*-fused system **3.4**.

More recently, chromeno[4,3-*b*]pyrrolone derivatives have been made using a radical addition-cyclization-elimination reaction (Figure **3.3**). The synthesis of these tricyclic lactams start from the allylation of phenol **3.5** with K_2CO_3 and ethyl 4-bromobut-2-enoate to produce α,β-unsaturated ester **3.6**. The resulting oxime was refluxed in benzene with AIBN and Bu_3SnH, giving the *cis* (26 %) **3.7** and *trans* (24 %) **3.8** isomers, in a total of 50% yield. This reaction is tolerant to different substitution on the aromatic ring providing similar yields. Even though the yields are low, this method provides a concise way to make highly substituted chromeno[4,3-*b*]pyrrole derivatives.

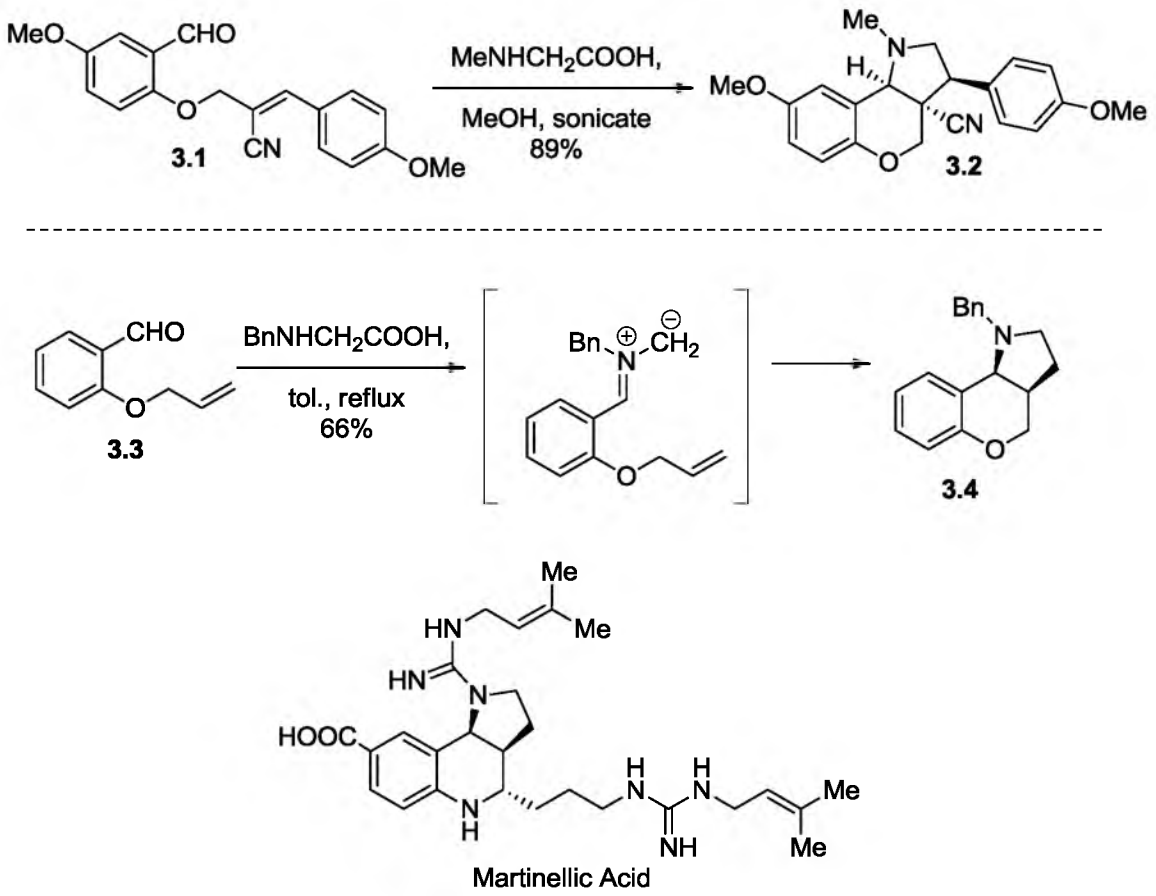


Figure **3.2**. Synthetic Approaches to the Chromeno [4,3-*b*] pyrroles

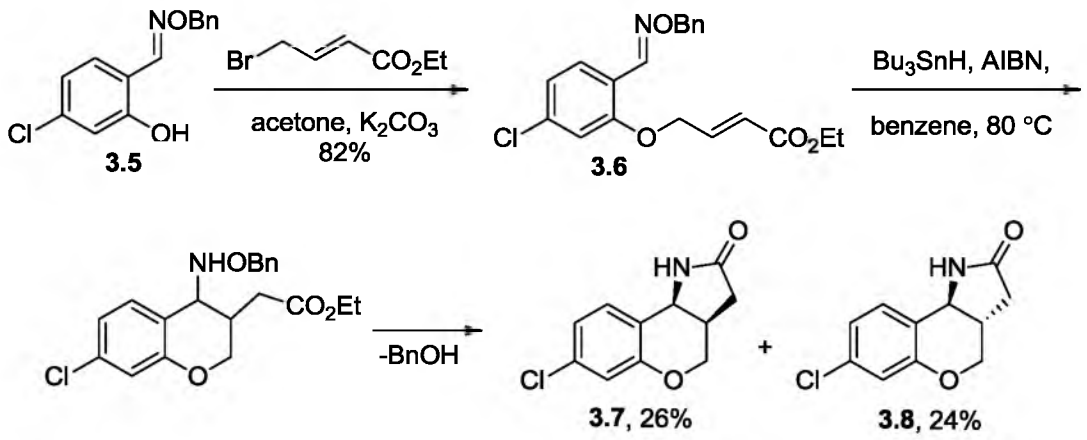


Figure 3.3. Synthesis of Chromeno [4,3-*b*] pyrrolone

The chromeno[4,3-*c*]pyrrole core has only been studied in a handful of peer reviewed articles[6] and is patented in various accounts.[7] Studies have shown that this particular motif is a selective dopamine D3 receptor antagonist potentially useful in treating psychotic disorders without neurological and endocrine side effects. Like the previously described synthesis of chromeno[4,3-*b*]pyrroline, a [3 + 2] cycloaddition was applied by the Lavielle group to construct the pyrrole of the chromeno[4,3-*c*]pyrrole system (Figure **3.4**, part **A**). The synthesis began with an intermolecular 1,3-dipolar cycloaddition of the activated double bond of (*E*)-methyl 3-(2-methoxyphenyl)acrylate with an azomethine ylide to give the *cis* pyrrolidine **3.10**. The methyl ester was then reduced with LAH and the methyl group was removed to give diol **3.11**. A Mitsunobu reaction using DEAD and PPh_3 would complete the chromeno[4,3-*b*]pyrroline ring system **3.12**. During Abbott's process scale synthesis of Fiduxosin, an asymmetric [3+2] cycloaddition is utilized to install the pyrrolidyl ring system (Figure **3.4**, part **B**).[8] The cycloaddition uses the ylide derived from **3.14**, which reacts with coumarin **3.13** in the presence of a catalytic amount of TFA to give the desired lactone **3.15** as a 1.5:1.0 ratio of epimers. These stereoisomers are separated

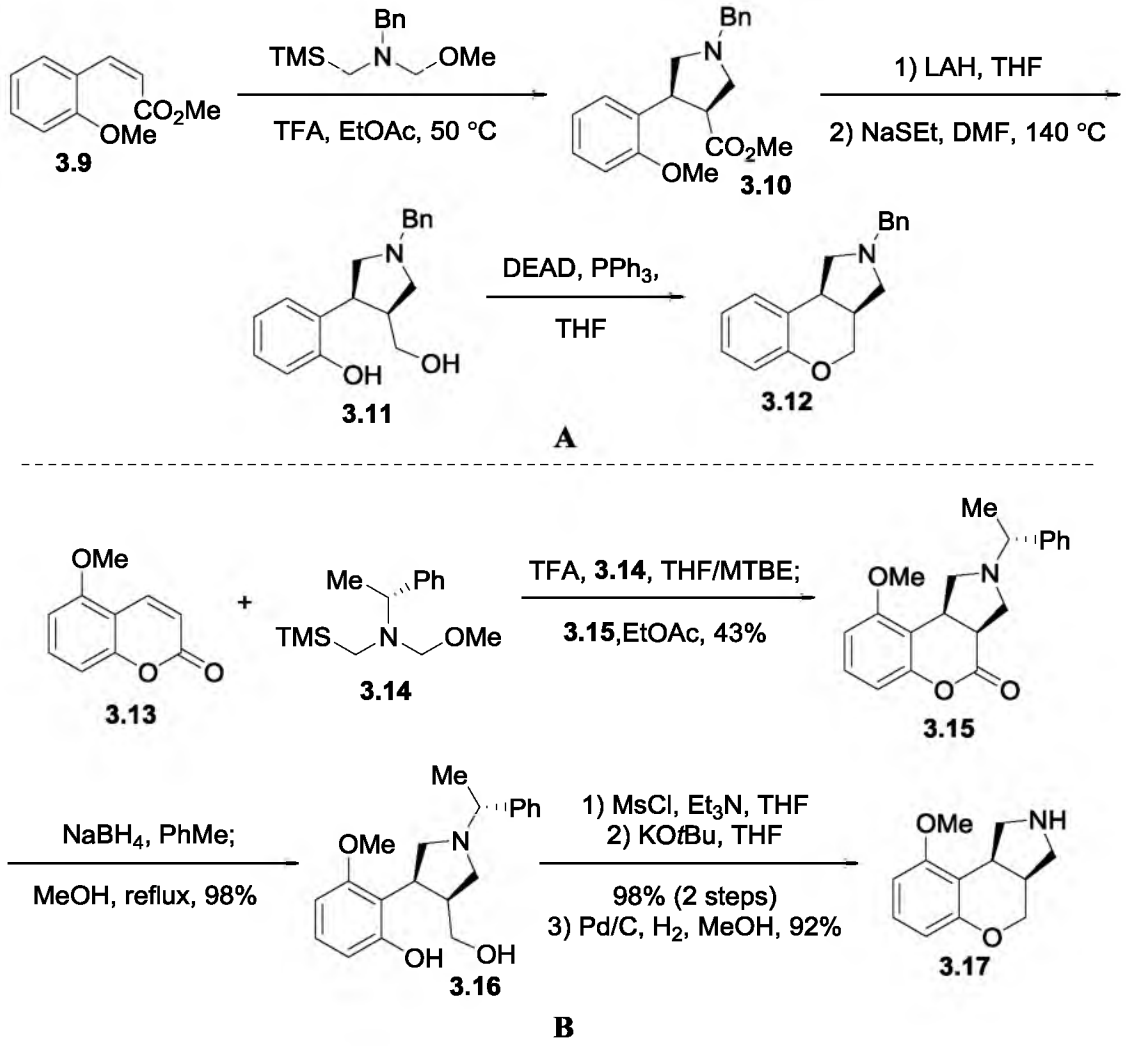


Figure 3.4. Synthesis of Chromeno [3,4-*c*] pyrrole Core by Lavielle (A) and Abbott (B)

using crystallization, giving high enantiomeric purity with an overall yield of 43% of chromenopyrroline **3.15**. Reduction of the lactone, followed by a methanol quench gave diol **3.16**. Mesylation of the primary alcohol, displacement of the mesylate with the phenol, and removal of the chiral axillary gave chromeno[4,3-*c*]pyrrole **3.17**. This synthesis improves the Lavielle group's synthesis by applying an intermolecular asymmetric 1,3-dipolar cycloaddition providing process scale amounts of **3.17**.

The Previous Synthetic Approaches

In 1970, the Oppolzer group reported the first example of the synthesis of a chromeno[3,4-*b*]pyrrole core.[9] This paper focused on the development of a 1,3-dipolar cycloaddition of nitrones and olefins to construct isoxazolidines. The route is shown in Figure **3.5A** and does not contain all necessary reagents and yields, because they were not diclosed in the paper. The synthesis starts with the addition of phenol **3.18** into oxiranemethanol to give diol **3.19**. Oxidative cleavage followed by condensation with methyl hydroxylamine gave nitrone **3.20**. Upon heating the nitrone, a [3+2] cycloaddition with an α,β-unsaturated ester takes place to provide the *cis* isoxazolidine **3.21**. The ethyl ester is then reduced and the resulting alcohol tosylated to produce tosyl ester **3.22**. Subjecting the isoxazolidine to hydrogenation conditions breaks the N-O bond, the resulting free amine then displaces the –OTs affording chromeno[3,4-*b*]pyrrole **3.23**.

The chromeno[3,4-*b*]pyrrole core was patented in 1996 by Novo Nordisk pharmaceuticals as a D3 dopamine receptor selective ligand.[10] Studies have shown that the D3 receptor is involved in neuropsychiatric disorders such as schizophrenia, drug addiction, depression and Parkinson's disease.[11] An example of the synthesis of a chromeno[3,4-*b*]pyrrole analog is given in the patent and is shown in Figure **3.5B**. The synthesis starts from chromanone **3.24**, which could be constructed in 4 steps following a literature procedure.[12] The condensation of the ketone **3.24** with propylamine provided enamine **3.25**. Formation of the pyrrolidine ring was accomplished by the reaction of enamine **3.25** with 1-bromo-chloroethane under basic conditions to provide tricyclic core **3.26**. The enamine was reduced using Adam's catalyst, followed by the isolation of chromeno[3,4-*b*]pyrrole core as the hydrochloride salt **3.27** in 31% yield over 2 steps.

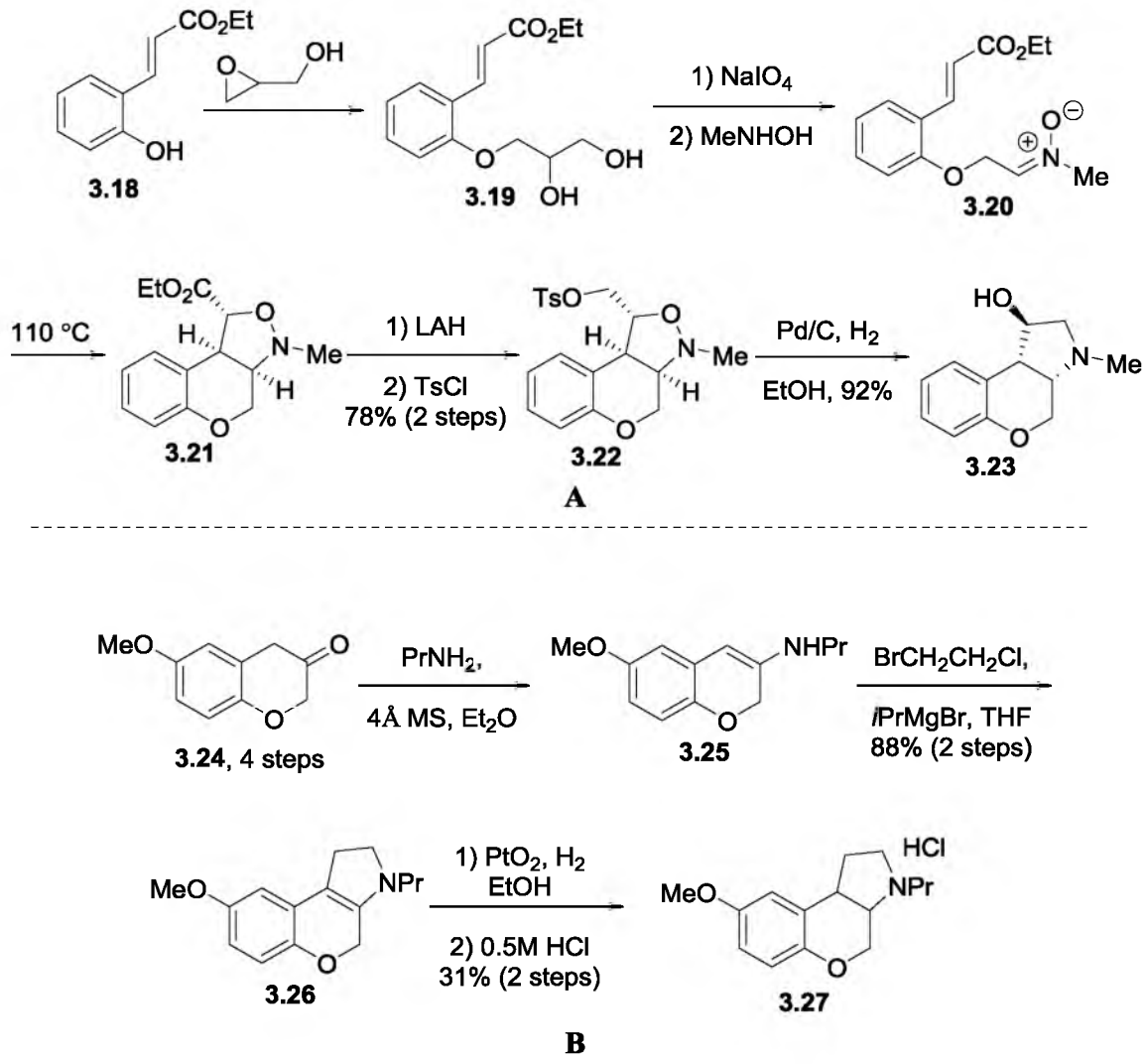


Figure **3.5**. Oppolzer's (A) and Novo Nordisk's Design (B)

Results and Discussion

Collaboration between the Keck group and Cephalon pharmaceuticals began in 2008. One of the projects was to design and synthesize chromeno[3,4-*b*]pyrrole since there were very few published examples of its core construction. The Keck group was told very little about the biological significance of this scaffold, only that it would be used as a PKC modulator. 2 different routes were explored and are shown in the following sections.

The Construction of the Chromeno[3,4-*b*]pyrrole Core (Route I)

The chromeno[3,4-*b*]pyrrole system **3.29** was envisioned to be constructed through an intramolecular stannyl radical mediated addition cyclization reaction from oxime/ester **3.30** (Figure **3.6**, part **A**). This reaction would construct both the six and five fused ring of the tricyclic core. The cyclization precursor **3.30** would be synthesized from 2-hydroxybenzaldehyde using a Horner-Wadsworth-Emmons and alkylation reactions from commercially available phenol **3.31**.

The synthesis started with the alkylation of phenol **3.31** with allyl bromide in the presence of K_2CO_3. The aldehyde **3.32** is then transformed into the α,β-unsaturated ester using ethyl 2-(diethoxyphosphoryl)acetate and sodium hydride to provide **3.33** as an 18:1 mixture of geometric isomers. The terminal olefin was cleaved using ozonolysis and the resulting aldehyde was converted to oxime ether **3.35**. An intramolecular radical cyclization reaction was expected between oxime ether and α,β-unsaturated ester using the tributyl stannyl radical generated from Bu_3SnH and AIBN. This reaction would form the C3-C4 bond and the resulting free amine would add into the ester to provide the fused pyrrolidine **3.29** (Figure **3.7**, part **B**). Unfortunately, these conditions only provided

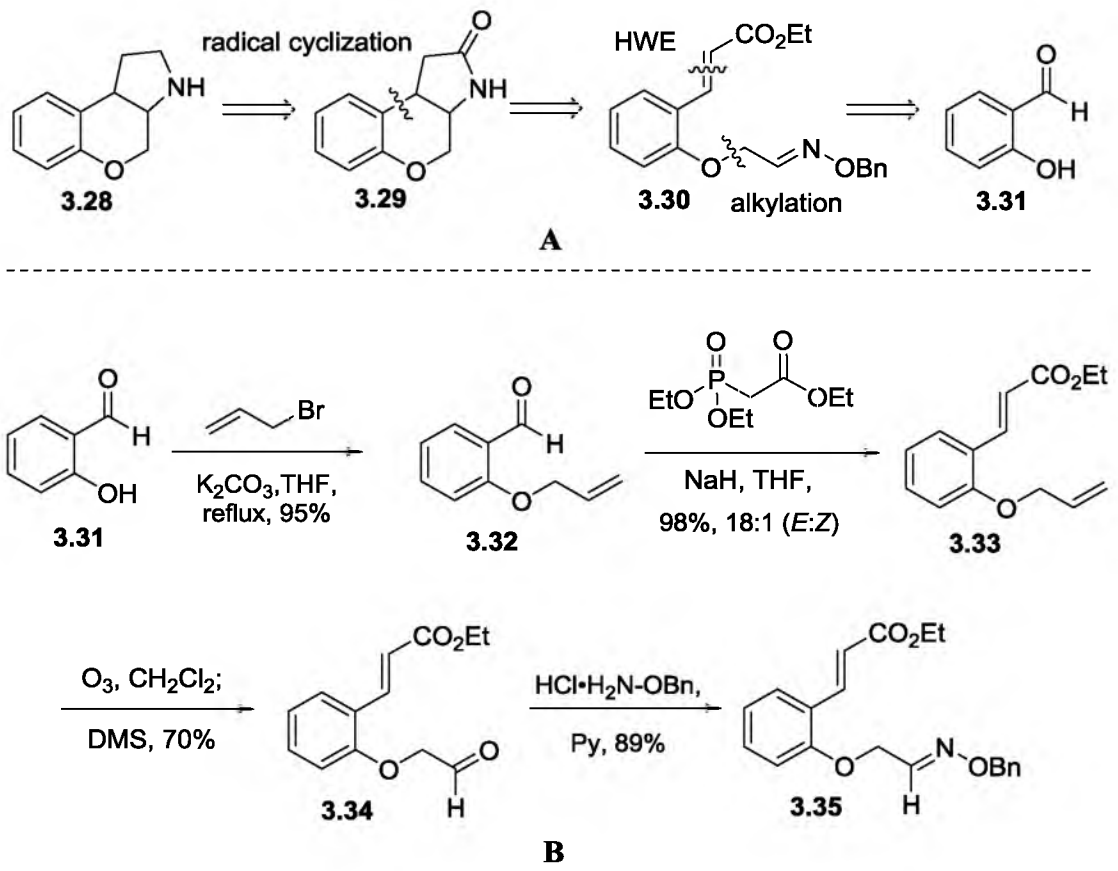


Figure **3.6**. Retrosynthetic Analysis (A) and Oxime Ether **3.35** (B)

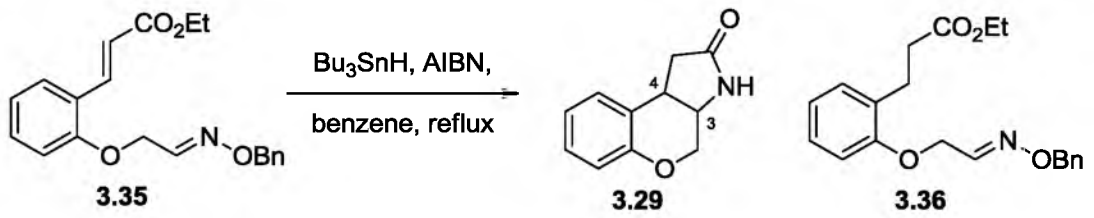


Figure 3.7. Intramolecular Radical Cyclization

the 1,4- reduction product **3.36** with no evidence of the desired compound **3.29**. Similar results were observed when **3.35** was subjected to samarium(II) diiodide conditions. With these unfortunate observations, a tactical change was needed to construct the chromeno[3,4-b]pyrrole system.

The Construction of the Chromeno[3,4-*b*]pyrrole Core (Route II)

The chromeno[3,4-*b*]pyrrole ring system **3.28** was envisioned to be constructed by an intramolecular radical or Heck cyclization, as shown in Figure **3.8**. The aryl iodide **3.37** would be formed by a Mitsunobu etherfication between 2-iodophenol and 2-hydroxymethyl-3-pyrroline **3.39**. This retrosynthetic plan allows interchanging of the phenol coupling partner providing diversification on the benzene ring.

Formation of the chromeno[3,4-*b*]pyrrole ring system began using a previously developed procedure to 2-hydroxymethyl-3-pyrroline **3.39** (Figure **3.9**, part **A**).[13] The

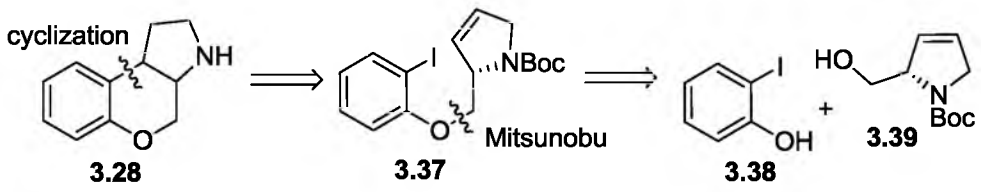


Figure 3.8. Retrosynthetic Analysis

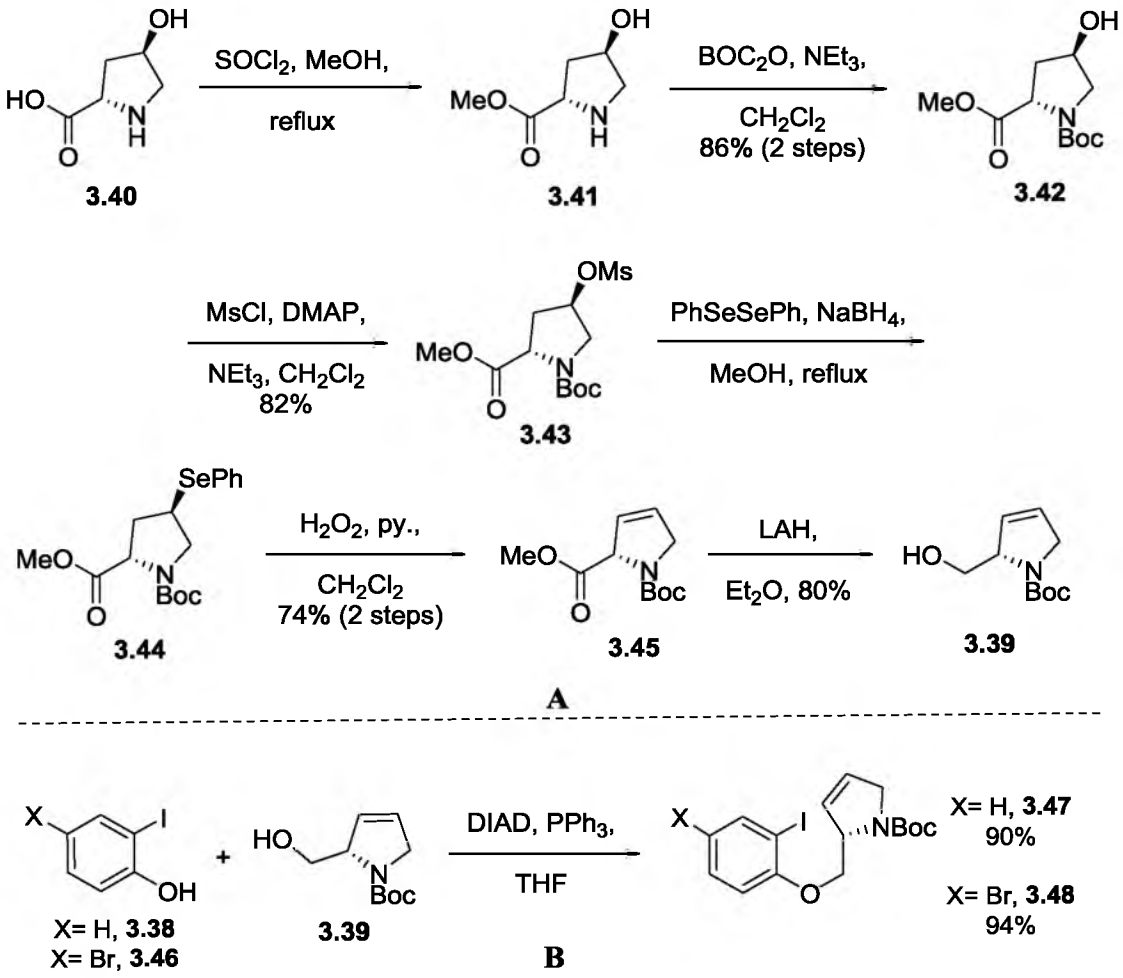


Figure 3.9. 2-hydoxymethyl-3-pyrroline (A) and Mitsunobu Coupling (B)

sequence started with the esterification of commercially available *trans*-4-hydroxy-L-proline, which was achieved using thionyl chloride and methanol to give the methyl ester. The pyrrolidine amine was BOC protected using BOC_2O to afford compound **3.42** in 86 % yield over 2 steps. The secondary alcohol was mesylated using MsCl and catalytic DMAP. Displacement of the mesylate with phenylselenide using diphenylselenide/$NaBH_4$ afforded the phenylselenide intermediate **3.44**. Oxidation of the phenylselenide with hydrogen peroxide and pyridine gave the phenylselenoxide which underwent *syn*-elimination to give

the olefin **3.45** as a single regioisomer in 74 % yield over 2 steps. Reduction of the ester with LAH in Et_2O afforded the desired precursor alcohol **3.39**.

2-hydroxymethyl-3-pyrroline was combined with either 2-iodophenol or 4-bromo-2-iodophenol using a Mitsunobu-type reaction providing **3.47** and **3.48** in good yields. The phenol **3.46** was made by the treatment of 4-bromophenol with NaI, NaOH, and NaOCl in methanol (Figure **3.9**, part **B**).[14]

After producing the tethered aryl iodide **3.47**, 2 types of cyclization reactions were investigated. First, a samarium mediated 6-*exo-trig* cyclization to give the chromeno[3,4-b]pyrrole ring system was explored.[15] The *cis* fused ring system is expected based on previous observation.[16] Unfortunately, the reduction of the alkyl iodide **3.47** with samarium (II) iodide in THF/HMPA produced both the desired product **3.49** and reduced product **3.50** in almost equal amounts (Figure **3.10**, part **A**). After a failed attempt using samarium(II) diiodide, a Heck coupling was explored. The Heck cyclization did not occur using common conditions with $Pd(OAc)_2$, Et_3N, PPh_3, and DMF at 100°C. In the literature, a methodology was developed for the intermolecular coupling of 2,5-dihydropyrroles and aryl iodides using $Pd(OAc)_2$, Ag_2CO_3, P(*o*-tol)$_3$, and (*i*Pr)$_2$NEt as single regioisomers.

Applying these conditions to **3.47**, the intramolecular Heck cyclization of **3.47** gave the desired chromeno[3,4-*b*]pyrrole core **3.51** (Figure **3.10**, part **B**). A single olefin regioisomer was observed in accordance with previous reported results. Additionally, these conditions tolerated a bromide in the 4-position allowing further functionalization giving chromeno[3,4-*b*]pyrrole **3.52** on a gram scale. Further manipulations of **3.54** were explored (Figure **3.10**, part **C**). The reduction of the enamine functionality was accomplished using Adams catalyst and H_2 in acetone to selectively give **3.53** without compromising the aryl

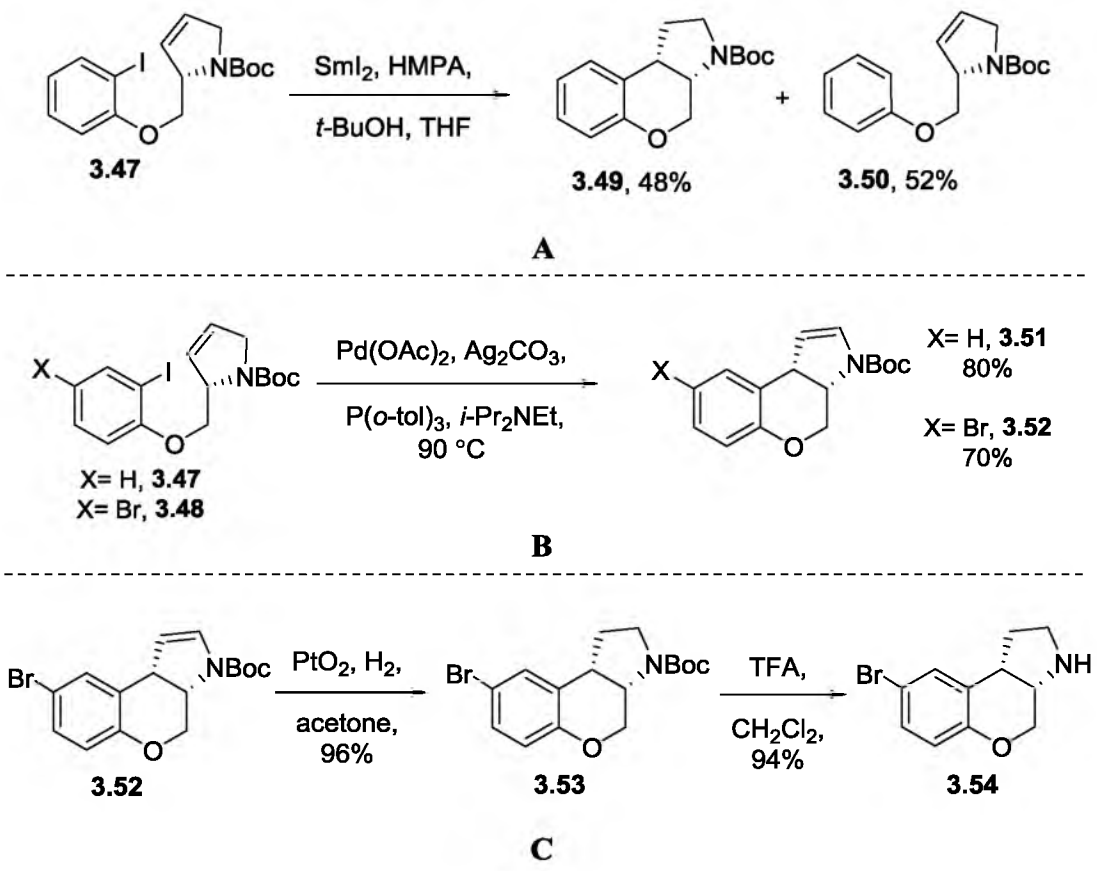


Figure 3.10. Samarium Mediated (A), Heck Cyclization (B), and Reduction/Deprotection (C)

bromide. The last step in this sequence was the removal of the BOC protecting group using TFA in CH_2Cl_2 to provide amine **3.54**.

After the synthesis of the chromeno[3,4-b]pyrrole core **3.52**, its structure was further confirmed by X-ray crystallographic analysis. This heavy atom X-ray crystal structure verified the absolute configuration at the *cis* ring fusion. Crystals of **3.52** were monoclinic having all dimensions of a = 7.4043(2) Å, b = 5.55780(10) Å, c = 18.9203(6) Å, space group of $P2_1$. The ORTEP diagram of this structure is shown in Figure **3.11**.

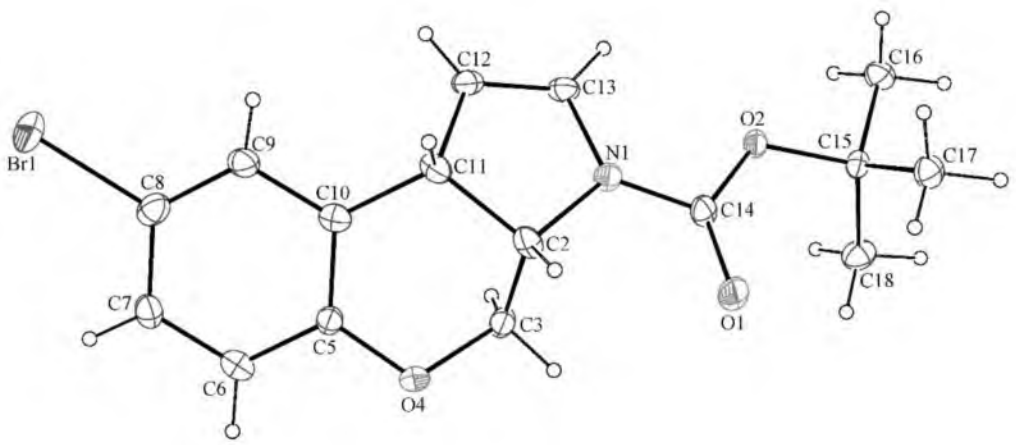


Figure **3.11**. Structure of 3.52 by X-ray Analysis

Conclusion

In conclusion, this sequence demonstrated a viable route for a multigram synthesis of the biologically useful intermediate **3.52**. This synthesis includes the incorporation of stereochemistry starting from the cheap commercially available starting material *trans*-4-hydroxy-L-proline. The Heck cyclization provided a robust method to construct the chromeno[3,4-b]pyrrole core. The versatility of this synthesis allows the preparation of various analogs by incorporating different substituents on the phenol coupling partner. This system can be further diversified independently at the amine position.

Experimental Section

General Experimental Procedures, Materials, and Instrumentation

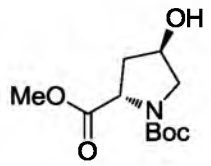
Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966).[1] *N,N*-diisopropylethylamine, HMPA, pyridine, Et_3N, EtOAc, and CH_2Cl_2 were distilled from

CaH_2. All other reagents were used without further purification. Yields were calculated for material judged homogenous by thin phase chromatography and nuclear magnetic resonance (NMR). Thin layer chromatography was performed on Merck Kieselgel 60 Å F_{254} plates or Silicycle 60Å F_{254} eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethenolic solution of 12-molybdophosphoric acid, 4-anisaldehyde, or an aqueous potassium permanganate solution. Flash column chromatography was performed with Silicycle flash silica gel 40 – 63 μm slurry packed with hexanes in glass columns. Glassware for reactions was oven dried at 125 °C and cooled under a dry nitrogen atmosphere prior to use. Liquid reagents and solvents were introduced by oven dried syringes through septum-sealed flasks under a nitrogen atmosphere. Nuclear magnetic resonance spectra were acquired at 500 MHz for ^1H and 125 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^1H NMR) spectra are reported in parts per million relative to the signal residual $CDCl_3$ at 7.27 ppm. Chemicals shifts for carbon nuclear magnetic resonance (^{13}C NMR and DEPT) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.23 ppm. Chemical shifts of the unprotonated carbons ('C') for DEPT spectra were obtained by comparison with the ^{13}C NMR spectrum. The abbreviations s, d, dd, ddd, dddd, dq, t, and m stand for the resonance multiplicity singlet; doublet; doublet of doublets; doublet of doublet of doublets; doublet of doublet; of doublet of doublets; doublet of quartet; triplet; and multiplet, respectively. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length. Specific rotations ($[\alpha]_D^{20}$, Unit: $°cm^2/g$) are based on the equation $\alpha = (100 \cdot \alpha)/(l \cdot c)$ and are reported as unitless numbers where the concentration c was in g/l00 mL and the path length l was in decimeters. Mass spectrometry was performed at the mass

spectrometry facility of the Department of Chemistry at The University of Utah on a double focusing high resolution mass spectrometer. Elemental analyses were performed by an out-of-house commercial analytical laboratory. Compounds were named using ChemDraw 11.0.1.

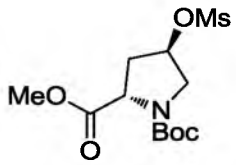
Experimental Procedures and Analytical Data for **3.39** and **3.46**

The compounds **3.42**, **3.43**, **3.45**, and **2.39** were previously prepared and are reported in the literature.[13] The synthesis of pyrrole **2.39** was repeated on a larger scale to assess these for use in the present work. The procedure to compounds **3.42** and **3.**45 were altered by purification using recrystallization instead of flash chromatography. Compound **3.46** was also previously prepared and are reported in the literature.[14] The experimental procedure and analytical data for pyrrole **2.39** and aryl iodide **3.46** are reproduced here for the convenience of those who may need to repeat this work.



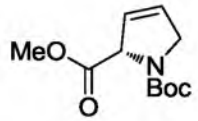
(2*S*,4*R*)-1-tert-butyl-2-methyl-4-hydroxypyrrolidine-1,2-dicarboxylate (3.42).[13] To a stirring solution of *trans*-4-hydroxy-L-proline (50.3 g, 383 mmol, 1.0 equiv) in MeOH (480 mL) in a 1 L rb flask at 0 ºC, was added $SOCl_2$ (33.5 mL, 460 mmol, 1.2 equiv). The reaction was stirred for 2 h at 0 °C, then for 2 h at reflux. The solution was cooled to rt and concentrated under reduced pressure. The crude ester was taken directly onto the next reaction without further purification.

To a stirring solution of this ester in CH_2Cl_2 (1.0 L) in a 2 L rb flask at 0 °C, was added Et_3N (162 mL, 1.15 mol, 3.0 equiv). Stirring was continued for 5 min, and a solution of Boc_2O (100 g, 460 mmol, 1.2 equiv) in CH_2Cl_2 (200 mL) was then added to the reaction mixture over 1.5 h via an addition funnel. The reaction was allowed to proceed for 15 h at rt. The organic phase was washed with aqueous $NaHSO_3$ solution (2 × 600 mL of 1N), with aqueous citric acid solution (600 mL of 10%), and with brine (600 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by recrystallization in EtOAc/hexanes. The resulting white solid was filtered and washed with ice cold hexanes to afford **3.42** (80.6 g, 86%). Analytical data: 1.3:1.0 mixture of rotamers; R_f = 0.21 (50% EtOAc/hexanes); mp 92°-94°; 500 MHz ^{1}H NMR ($CDCl_3$) δ 4.53-4.48 (br s, 1H), 4.45 (t, *J* = 7.8 Hz, 1H, minor), 4.40 (t, *J* = 7.1 Hz, 1H major), 3.75 (s, 3H, minor), 3.73 (s, 3H, major), 3.66 (d, *J* = 3.9 Hz, 1H, minor), 3.63 (d, *J* = 3.9 Hz, 1H major), 3.56 (d, *J* = 11.7 Hz, 1H, major), 3.46 (d, *J* = 11.7 Hz, 1H minor), 2.35-2.22 (m, 1H), 2.14-2.04 (m, 1H), 1.46 (s, 9H, minor), 1.42 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 174.0 (major), 173.8 (minor), 154.9 (minor), 154.3 (major), 80.7(major), 80.6 (minor), 70.3 (minor), 69.6 (major), 58.3 (major), 57.8 (minor), 55.0 (minor), 54.9 (major), 52.6 (minor), 52.4 (major), 39.4 (major), 38.7 (minor), 28.7 (minor), 28.5 (major); 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 52.5 (minor), 52.3 (major), 28.6 (minor), 28.5 (major); CH_2 δ 54.9 (minor), 54.8 (major), 39.3 (major), 38.7 (minor); CH δ 70.3 (minor), 69.5 (major), 58.2 (major), 57.7 (minor); CH_0 δ 174.0 (major), 173.8 (minor), 154.9 (minor), 154.3 (major), 80.7 (major), 80.6 (minor).



(2*S*,4*R*)-1-tert-butyl 2-methyl 4-(methylsulfonyloxy)pyrrolidine-1,2-dicarboxylate (3.43).[13] To a stirring solution of alcohol **3.42** (39.6 g, 161 mmol, 1.0 equiv) in CH_2Cl_2 (500 mL) in a 1 L rb at 0 °C, were added DMAP (5.90 g, 48.0 mmol, 0.3 equiv) and Et_3N (45.0 mL, 323 mmol, 2.0 equiv), followed by a solution of MsCl (25.0 mL, 323 mmol, 2.0 equiv) in CH_2Cl_2 (40 mL) over 30 min via an addition funnel. TLC analysis after stirring at rt for 3 h indicated complete consumption of the starting material. The organic phase was washed with H_2O (200 mL), with aqueous $KHSO_4$ solution (200 mL of 10%), with aqueous saturated $NaHCO_3$ solution (200 mL), and brine (200 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by recrystallization in EtOAc/hexanes. The resulting white solid was filtered and washed with ice cold hexanes to afford **3.43** (43.0 g, 82%). Analytical data: 1.0:1.7 mixture of rotamers; R_f = 0.29 (50% EtOAc/hexanes); mp 105°-108°; 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.20-5.35 (m, 1H), 4.48 (t, J = 7.8 Hz, 1H, minor), 4.41 (t, J = 8.3 Hz, 1H major), 3.86 (m, 1H, minor), 3.85 (m, 1H, major), 3.82-3.73 (m, 4H), 3.06 (s, 3H), 2.71-2.63 (m, 1H, major), 2.61-2.54 (m, 1H, minor), 1.47 (s, 9H, minor), 1.43 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.9 (major), 172.6 (minor), 154.1 (minor), 153.5 (major), 81.0, 78.5 (minor), 78.2 (major), 57.6 (major), 57.3 (minor), 52.7, 52.5 (minor), 52.4 (major), 38.9 (major), 38.8 (minor), 37.6 (major), 36.5 (minor), 28.5 (minor), 28.3 (major); 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 52.6 (minor), 52.5 (major), 38.9, 28.5 (minor), 28.4 (major); CH_2 δ 52.7 (minor), 52.4 (major), 37.6 (major), 36.5 (minor); CH δ 78.5 (minor),

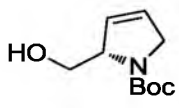
78.2 (major), 57.6 (major), 57.3 (minor); CH_0 δ 172.9 (major), 172.6 (minor), 154.1 (minor), 153.5 (major), 81.0.



((*S*)-1-tert-butyl 2-methyl 1H-pyrrole-1,2(2H,5H)-dicarboxylate (3.45).[13] To a stirring solution of mesylate **3.43** (43.0 g, 133 mmol, 1.0 equiv) in MeOH (450 mL) in a 1 L rb flask at 0 °C, was added diphenyl diselenide (24.9 g, 79.9 mmol, 0.6 equiv). Stirring was continued for 5 min, and $NaBH_4$ (6.60 g, 173 mmol, 1.3 equiv) was added in 4 large portions over 20 min. TLC analysis after stirring at reflux for 12 h indicated complete consumption of the starting material. The reaction mixture was quenched by pouring the mixture into a 2 L Erlenmeyer flask containing a stirring solution of H_2O (500 mL) and CH_2Cl_2 (500 mL). The phases were separated and the organic phase was washed with H_2O (2 × 100 mL), with aqueous HCl solution (2 × 100 mL of 1N), and with brine (100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude selenide was taken directly onto the next reaction without further purification.

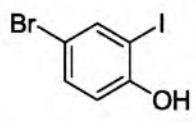
To a stirring solution of this selenide in CH_2Cl_2 (450 mL, 0.3M) in a 1 L rb flask at 0 °C, was added pyridine (15.0 mL, 186 mmol, 1.4 equiv), followed by a solution of aqueous H_2O_2 solution (23.0 mL of 30%, 200 mmol, 1.5 equiv) over 30 min via an addition funnel. TLC analysis after stirring at rt for 2 h indicated complete consumption of the starting material. The organic phase was washed with aqueous citric acid solution (150

mL of 10%), with aqueous saturated Na_2SO_3 solution (150 mL), and with brine (150 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with 5% and 10% EtOAc/hexanes to afford **3.45** (22.5 g, 74%) as a clear liquid. Analytical data: 1.0:1.6 mixture of rotamers; $R_f = 0.37$ (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 6.00 (dddd, J = 4.4, 2.5, 2.5, 2.5 Hz, 1H, major), 5.95 (dddd, J = 3.9, 2.0, 2.0, 2.0 Hz, 1H, minor), 5.76 (dddd, J = 4.4, 2.5, 2.5, 2.5 Hz, 1H, minor), 5.72 (dddd, J = 4.4, 2.4, 2.4, 2.4 Hz, 1H, major), 5.26 (dddd, J = 4.5, 2.4, 2.4, 2.4 Hz, 1H, minor), 4.97 (dddd, J = 4.9, 2.4, 2.4, 2.4 Hz, 1H, major), 4.30-4.15 (m, 2H), 3.75 (s, 3H, minor), 3.74 (s, 3H, major), 1.49 (s, 9H, minor), 1.44 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.1 (major), 170.8 (minor), 153.9 (minor), 153.4 (major), 124.8 (minor), 124.7 (major), 80.2 (major), 80.1 (minor), 66.6 (major), 66.3 (minor), 53.6 (minor), 53.3 (major), 52.3 (minor), 52.2 (major), 28.5 (minor), 28.3 (major); 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 52.2, 28.5 (minor), 28.4 (major); CH_2 δ 53.6 (minor), 53.4 (major); CH δ 129.5 (minor), 129.4 (major), 124.8 (minor), 124.7 (major), 66.7 (major), 66.3 (minor); CH_0 δ 171.1 (major), 170.8 (minor), 153.9 (minor), 153.4 (major), 80.2 (major), 80.2 (minor).



(*S*)-tert-butyl 2-(hydroxymethyl)-2,5-dihydro-1H-pyrrole-1-carboxylate (3.39).[13] To a stirring solution of ester **3.45** (22.5 g, 99.1 mmol, 1.0 equiv) in ether (500 mL) in a 1 L rb flask at 0° C, was added lithium aluminum hydride (4.10 g, 109 mmol, 1.10 equiv) in five portions over 30 mins. TLC analysis after stirring at rt for 1 h indicated complete consumption of the starting material. The reaction mixture was quenched by the

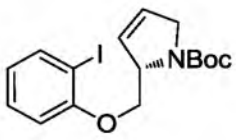
addition of H_2O (5 mL), with aqueous NaOH solution (5 mL of 15%), and then with an additional amount of H_2O (15 mL). Stirring was continued for 1 h at rt. The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography using 25% EtOAc/hexanes providing the alcohol **3.39** (15.8 g, 80%) as a clear liquid. Analytical data: 1.0:1.6 mixture of rotamers; R_f = 0.30 (30% EtOAc/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.97-5.90 (m, 1H, minor), 5.84-5.79 (m, 1H, major), 5.72-5.67 (m, 1H, minor), 5.62 (m, 1H, major), 4.78-4.72 (m, 1H, major), 4.66 (d, *J* = 9.3 Hz, 1H), 4.65-4.57 (m, 1H, minor), 4.22-4.16 (m, 1H, major), 4.10 (ddd, *J* = 5.37, 1.95, 1.95 Hz, 1H, major), 4.07 (ddd, *J* = 4.88, 1.95, 1.95, Hz, 1H, minor), 3.97 (t, *J* = 10.7 Hz, 1H), 3.69-3.62 (m, 1H, minor), 3.57 (ddd, *J* = 11.5, 7.3, 1.7, 1H, major), 1.51 (s, 9H, minor), 1.50 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 156.6, 127.8 (minor), 127.3 (minor), 127.0 (major), 126.9 (major), 80.7 (major), 80.4 (minor), 67.8 (minor), 67.2 (major), 66.4 (minor), 64.6 (minor), 54.4 (major), 54.3 (minor), 28.7; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.6; CH_2 δ 67.2 (major), 64.6 (minor), 54.4 (major), 54.2 (minor); CH δ 127.7 (minor), 127.3 (minor), 127.0 (major), 126.9 (major), 67.7 (major), 66.4 (minor); CH_0 δ 156.6, 80.7 (major), 80.4 (minor).



4-bromo-2-iodophenol (3.46).[14] To a stirring solution of 4-bromophenol (30. 8 g, 179 mmol, 1.0 equiv) in 7:5 MeOH/H_2O (600 mL) in a 2 L rb flask at 0 °C, was added NaI (26.4 g, 179 mmol, 1.0 equiv) and NaOH (7.20 g, 179 mmol, 1.0 equiv). Stirring was continued for 5 min, and an aqueous NaOCl solution (223 mL of 6%, 170 mmol, 1.0 equiv)

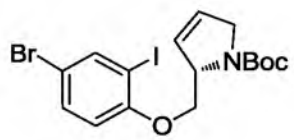
was then added to the reaction mixture over 30 min via an addition funnel. TLC analysis after stirring at rt for 1 h indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (50 mL), and aqueous KH_2PO_4 solution (300 mL of 10%). The resulting mixture was diluted with 80% EtOAc/hexanes (3 × 300 mL), the phases were separated, and the aqueous phase was extracted with 80% EtOAc/hexanes (2 × 300 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with 5% CH_2Cl_2/hexanes to provide phenol **3.46** (37.8 g, 71%) as a white solid: R_f = 0.36 (50% CH_2Cl_2/hexanes); mp 70°-72°; 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.77 (d, *J* =2.4 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 5.25 (s, 1H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 154.5, 140.1, 133.4, 116.6, 113.4, 86.5.

Experimental Procedures and Analytical Data Toward for **3.52** amd **3.54**



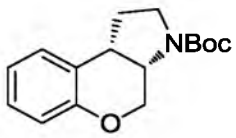
(*S*)-tert-butyl 2-((2-iodophenoxy) methyl)-2,5- dihydro-1H- pyrrole-1-carboxylate (3.47). To a stirring solution of alcohol **3.39** (360 mg, 1.81 mmol, 1.0 equiv) in THF (9 mL) in a 25 ml rb flask, was added 2-iodophenol (438 mg, 1.99 mmol, 1.1 equiv) and PPh_3 (711 mg, 2.71 mmol, 1.5 equiv). The resulting solution was cooled to 0 °C and diisopropyl azodicarboxylate (0.72 mL, 3.62 mmol, 2.00 equiv) was added dropwise. TLC analysis after stirring at rt for 5 h indicated complete consumption of the starting material. The reaction mixture was quenched by transfer into a 250 mL separatory or funnel that

contained a mixture of a 50 % EtOAc/hexanes (25 mL) and with aqueous NaOH solution (20 mL of 15%). The aqueous phase was extracted with 50% EtOAc/hexanes (2 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with 5%, 10%, and 20% EtOAc/hexanes providing a mixture of product **3.47** (450 mg, 62%) as a colorless oil. Analytical data: 1.0:1.2 mixture of rotamers; R_f = 0.75 (25% EtOAc/hexanes); $[\alpha]_D^{20}$ = -205 (*c* = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H, minor), 7.74 (d, *J* = 7.7 Hz, 1H, major), 7.32-7.24 (m, 1H), 6.88 (d, *J* = 8.3 Hz, 1H, major), 6.82 (d, *J* = 7.8 Hz, 1H, minor), 6.71 (ddd, *J* = 15.9, 8.8, 7.7 Hz, 1H), 6.05-5.88 (m, 2H), 4.92-4.86 (m, 1H, major), 4.85-4.78 (m, 1H, minor), 4.38-4.31 (m, 1H, major), 4.31-4.28 (m, 1H, minor), 4.24-4.14 (m, 2H, major), 3.95 (dd, *J* = 7.3, 7.3 Hz, 1H, minor), 1.50 (s, 9H, minor), 1.48 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 157.4, 154.5 (major), 154.2(minor), 139.7 (minor), 139.5 (major), 129.7 (major), 129.6 (minor), 128.3 (minor), 128.1 (major), 127.3 (minor), 127.2 (major), 122.9 (minor), 122.7 (major), 112.5 (major), 112.3 (minor), 86.8 (minor), 86.5 (major), 80.3 (minor), 79.9 (major), 70.4 (minor), 69.1 (major), 63.4 (major), 63.1 (minor), 54.4 (major), 54.1 (minor), 28.8; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.8; CH_2 δ 70.4 (minor), 69.1 (major), 54.4 (major), 54.2 (minor); CH δ 139.7 (minor), 139.5 (major), 129.7 (major), 129.6 (minor), 128.3 (minor), 128.2 (major), 127.3 (minor), 127.2 (major), 112.5 (major), 112.3 (minor), 63.4 (major), 63.1 (minor); CH_0 δ 157.4, 154.5 (major), 154.2 (minor), 86.8 (minor), 86.5 (major), 80.3 (minor), 79.9 (major); IR (neat) 2974, 2865, 1694, 1475, 1398, 1250, 1173, 1123, 1018, 748 cm ^{1}; HRMS (ESI) calcd for $C_{16}H_{20}NO_3NaI$ (M+Na): 424.0386, found: 424.0394.



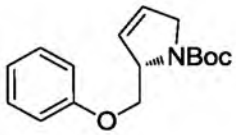
(*S*)-tert-butyl 2-((4-bromo- 2-iodophenoxy) methyl)-2,5-dihydro-1H-pyrrole-1-carboxylate (3.48). To a stirring solution of alcohol **3.39** (8.30 g, 41.7 mmol, 1.0 equiv.) in THF (300 mL) in a 500 mL rb flask at 0 °C, were added phenol **3.46** (24.9 g, 83.5 mmol, 2.0 equiv) and PPh_3 (14.2 g, 54.3 mmol, 1.3 equiv), followed by diisopropyl azodicarboxylate (10.8 mL, 54.3 mmol, 1.3 equiv) dropwise. TLC analysis after stirring at rt for 5 h indicated complete consumption of the starting material. The reaction mixture was quenched by transfer into a 1 L separatory funnel that contained a mixture of a 50 % EtOAc/hexanes (250 mL) and with aqueous NaOH solution (200 mL of 15%). The layers were separated and the aqueous layer was extracted with 50% EtOAc/hexanes (2 × 250 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with 5%, 10%, and 20% EtOAc/hexanes providing a mixture of product **3.48** (18.2 g, 94%) as a colorless oil. Analytical data: 1.0:1.3 mixture of rotamers; R_f = 0.48 (25% EtOAc/hexanes); $[\alpha]_D^{20}$ = -168 (*c* = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.86 (d, *J* = 2.4 Hz, 1H, minor), 7.84 (d, *J* = 2.4 Hz, 1H, major), 7.39 (dd, *J* = 1.9, 7.6 Hz, 1H, minor), 7.37 (dd, *J* = 2.4, 8.8 Hz, 1H, major), 6.75 (d, *J* = 8.8 Hz, 1H, major), 6.75 (d, *J* = 8.8 Hz, 1H, minor), 5.98-5.96 (m, 1H), 5.95-5.94 (m, 1H, minor), 5.93-5.89 (m, 1H, major), 4.90-4.84 (m, 1H, major), 4.83-4.78 (m, 1H, minor), 4.35-4.27 (m, 2H), 4.23-4.13 (m, 2H), 3.95 (dd, *J* = 8.8, 6.9 Hz, 1H, minor), 1.49 (s, 9H, minor), 1.48 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 156.9, 154.5 (minor), 141.5 (minor), 141.2 (major), 132.4 (major), 131.4 (minor), 128.0 (minor), 120.0 (major), 127.6 (minor), 127.5 (major), 113.6 (minor), 113.5

(minor), 113.3, 87.3 (major), 80.4 (minor), 80.1 (major), 70.6 (minor), 69.4 (major), 63.4 (major), 63.1 (minor), 54.4 (major), 54.2 (minor), 28.9 (minor), 28.8 (major); 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.9 (minor), 28.8 (major); CH_2 δ 70.7 (minor), 69.4 (major), 54.4 (major), 54.2 (minor); CH δ 141.5 (minor), 141.2 (major), 132.4 (major), 132.4 (minor), 128.0 (major), 127.6 (minor), 127.5 (major), 113.6 (major), 113.4 (minor), 63.4 (major), 63.1 (minor); CH_0 δ 159.9, 154.5 (major), 154.2 (minor), 113.3, 87.6 (minor), 87.3 (major), 80.4 (minor), 80.1 (major); IR (neat) 3081, 2974, 2929, 2905, 2866, 1693, 1626, 1561, 1459, 1399, 1332, 1279, 1247, 1173, 1124, 1039, 872, 802, 772, 716 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}NO_3NaBrI$ (M+Na): 501.9491, found: 501.9502.



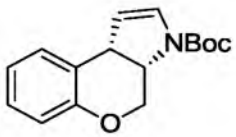
(3a*S*,9b*S*)-tert-butyl 1,3a,4,9b-tetrahydrochromeno [3,4-b]pyrrole -3(2H)-carboxylatee (3.49). To a stirring solution of SmI_2 (0.1 M solution in THF, 5.3 mL, 0.5 mmol, 3.0 equiv)[17] in a 25 ml rb flask, was added HMPA (0.4 mL, 2.5 mmol, 14.0 equiv). A solution of aryl iodide **3.47** (70 mg, 0.18 mmol, 1.0 equiv), *t*BuOH (0.50 μL, 0.53 mmol, 3.0 equiv), and THF (1 mL) was added dropwise via cannula, and rinsed with THF (2 × 0.25 mL). After 30 min, additional SmI_2 (0.1M solution in THF, 5.3 mL, 0.5 mmol, 3.0 equiv) and HMPA (0.4 mL, 2.5 mmol, 14.0 equiv) were added and the deep purple color persisted. TLC analysis showed consumption of the starting material after 6 h. The reaction mixture was quenched by transfer into a 250 mL separatory funnel that contained a mixture of a CH_2Cl_2 (50 mL) and pH 7 aqueous $NaKPO_4$ solution (20 mL). The organic phase was washed with H_2O (2 × 30 mL), brine (25 mL), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. Purification was accomplished by flash column chromatography using 10% EtOAc/hexanes provides the tricyclic **3.49** (23 mg, 48%) and dehalogenated **3.50** (25 mg, 52%) as clear liquids. Analytical data: 2.0:1.0 mixture of rotamers; R_f = 0.31 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ = -114.5 (*c* = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.22-7.08 (m, 2H), 7.00-6.85 (m, 2H), 4.43-4.31 (m, 1H), 4.23-4.14 (m, 1H, minor), 4.12-4.03 (m, 1H, major), 3.72 (ddd, *J* = 9.3, 9.3, 9.3 Hz, 1H, minor), 3.58 (ddd, *J* = 10.3, 10.3, 10.3 Hz, 1H, major), 3.53-3.33 (m, 3H), 2.52-2.35 (m, 1H), 2.01 (dddd, *J* = 20.5, 19.7, 9.8, 9.8 Hz, 1H), 1.51 (s, 9H, major), 1.49 (s, 9H, minor); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.2, 154.9 (minor), 154.5 (major), 129.7 (major), 129,6 (minor), 127.8 (major), 127.7 (minor), 124.3 (minor), 124.4 (major), 121.6 (major), 121.4 (minor), 117.2 (minor), 117.2 (major), 80.2 (major), 79.9 (minor), 65.2 (major), 55.0 (minor), 53.6 (minor), 53.3 (major), 45.7 (minor), 45.2 (major), 38.3 (major), 37.3 (minor), 33.5 (minor), 33.5 (major), 28.9; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.6; CH_2 δ 65.1 (major), 64.8 (minor), 45.5 (minor), 45.1 (major), 33.3 (minor), 32.4 (major); CH δ 129.6 (major), 129.5 (minor), 127.7 (major), 127.6 (minor), 121.4 (major), 121.3 (minor), 117.2 (minor), 117.0 (major), 53.5 (major), 53.1 (major), 38.0 (major), 37.2 (minor); CH_0 δ 173.2, 154.9 (minor), 154.5 (major), 124.4 (major), 80.2 (major), 79.9 (minor); IR (neat) 2974, 2878, 1693, 1583, 1489, 1455, 1394, 1231, 1176, 1122, 1044, 900, 758 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}NO_3Na$ (M+Na): 298.1419, found: 298.1422.



(*S*)-tert-butyl-2-(phenoxymethyl)-2,5-dihydro-1H-pyrrole-1-carboxylate)

(3.50). Analytical data: 1.2:1.0 mixture of rotamers; R_f = 0.38 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ = -195 (*c* = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.32-7.22 (m, 2H), 7.00-6.88 (m, 3H), 5.96-5.84 (m, 2H), 4.91-4.72 (m, 1H), 4.42-4.14 (m, 2H), 4.12-3.90 (m, 2H), 3.90 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1H, minor), 1.50 (s, 9H, major), 1.48 (s, 9H, minor); 125 MHz ^{13}C NMR ($CDCl_3$) δ 159.0 (major), 1548.9 (minor), 154.4 (major), 154.2 (minor), 129.5 (major), 129.5 (minor), 128.3, 126.9 (major), 126.6 (minor), 121.0 (major), 120.8 (minor), 114.9 (minor), 114.7 (major), 80.2 (minor), 79.7 (major), 69.5 (major), 68.4 (minor), 63.6 (minor), 63.2 (major), 54.1 (minor), 53.9 (major), 28.7; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.7; CH_2 δ 69.5(major), 68.2 (minor), 54.2 (minor), 53.9 (major); CH δ 129.5 (major), 129.5 (minor), 128.3, 126.9 (major), 126.6 (minor), 121.0 (major), 120.8 (minor), 114.9 (minor), 114.7 (major), 63.5 (minor), 63.2 (major); CH_0 δ 159.0 (major), 158.9 (minor), 154.4 (major), 154.2 (minor), 87.2 (minor), 79.7 (major); IR (neat) 2975, 2867, 1697, 1599, 1497, 1396, 1246, 1173, 1109, 1040, 754, 692 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}NO_3Na$ (M+Na): 298.1419, found: 298.1419.

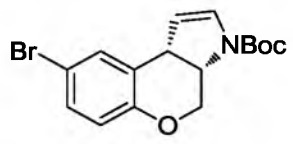


(3a*S*,9b*S*)-*tert*-butyl 3a,4-dihydrochromeno[3,4-*b*]pyrrole-3(9b*H*)-carboxylate

(3.51). To a stirring solution of aryl iodide **3.47** (75 mg, 0.19 mmol, 1.0 equiv) in DMF (2 mL), was added (*i*Pr)$_2$NEt (130 μL, 0.75 mmol, 4.0 equiv) in a 10 ml rb flask. N_2 gas was

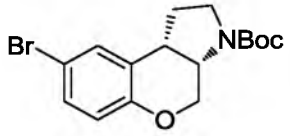
bubbled through the resulting solution for 1 h. Ag_2CO_3 (10 mg, 0.04 mmol, 0.2 equiv), tri-*o*-tolylphosphine (11 mg, 0.04 mmol, 0.2 equiv) and palladium(II) acetate (4 mg, 0.02 mmol, 0.1 equiv) were added in one portion. TLC analysis after stirring at 90 ºC for 26 h indicated complete consumption of the starting material. The mixture was cooled to rt then filtered through a small plug of Celite and washed with copious amounts of EtOAc. The organic phase was diluted with H_2O (10 mL), then the phases were separated and the aqueous phase was extracted with 20% EtOAc/hexanes (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with 10% EtOAc/hexanes providing the pure tricyclic **3.51** as a colorless oil (41 mg, 80%). Analytical data: 1.0:1.3 mixture of rotamers; R_f = 0.38 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ = -115.0 (*c* = 1.0, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.24-7.08 (m, 2H), 6.98 (dd, *J* = 13.7, 6.4 Hz, 1H), 6.91 (dd, *J* = 13.7, 6.4 Hz, 1H), 6.64-6.60 (m, 1H, minor), 6.48-6.44 (m, 1H, major), 5.20-5.16 (m, 1H, minor), 5.08-4.02 (m, 1H, major), 4.62 (ddd, *J* = 15.6, 10.3, 5.4 Hz, 1H), 4.58-4.50 (m, 1H, minor), 4.36 (d, *J* = 9.7 Hz, 1H, minor), 4.30 (d, *J* = 4.4 Hz, 1H, major), 4.21 (dd, *J* = 10.8, 4.4 Hz, 1H, major), 4.20-4.12 (m, 1H), 3.83 (dd, *J* = 9.8, 9.8 Hz, 1H, minor), 1.57 (s, 9H, minor), 1.50 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 156.0 (major), 155.9 (minor), 129.4 (major), 129.3 (minor), 129.2 (major), 129.1 (minor), 127.7, 124.7, 123.9, 122.3, 118.0 (major), 117.7 (minor), 112.2 (minor), 111.9 (major), 81.2, 65.3 (major), 64.8 (major), 56.4 (major), 55.5 (major), 42.9 (minor), 41.9 (major), 28.7; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.7; CH_2 δ 65.3 (major), 64.8 (major); CH δ 129.4 (major), 129.3 (minor), 129.2 (major), 129.1 (minor), 127.7, 118.0 (major), 117.7 (minor), 112.2 (minor), 111.9 (major), 56.4 (major), 55.5 (major), 42.9

(minor), 41.9 (major); CH_0 δ 156.0 (major), 155.9 (minor), 127.7, 126.4 (minor), 124.7, 123.9, 81.2; IR (neat) 2979, 2937, 2878, 1715, 1470, 1350, 1270, 1240, 1180, 1104, 1091 cm^{-1}; Anal. Calcd for $C_{16}H_{18}NO_3$: C, 70.31; H, 7.01; N, 5.12; O, 17.56. Found: C, 69.60; H, 5.08; N, 3.83; O, 3.82.



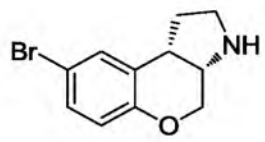
(3a*S*,9b*S*)-tert-butyl 8-bromo-3a,4- dihydrochromeno [3,4-b]pyrrole-3(9bH)-carboxylate (3.52). To a stirring solution of aryl iodide **3.48** (15.2 g, 32.8 mmol, 1.0 equiv) in DMF (330 mL), was added (*i*Pr)$_2$NEt (22.9 mL, 131 mmol, 4.0 equiv) in a 1 L rb flask. N_2 gas was bubbled through the resulting solution for 1 h. Ag_2CO_3 (1.80 g, 6.60 mmol, 0.2 equiv), tri-*o*-tolylphosphine (2.00 g, 6.60 mmol, 0.2 equiv) and palladium(II) acetate (0.70 g, 3.30 mmol, 0.1 equiv) were added in one portion. TLC analysis after stirring at 90 ºC for 90 h indicated complete consumption of the starting material. The mixture was cooled to rt then filtered through a small plug of Celite and washed with copious amounts of EtOAc. The organic phase was diluted with H_2O (500 mL), then the phases were separated and the aqueous phase was extracted with 25% EtOAc/hexanes (2 × 250 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with 2%, 5%, and 10% EtOAc/hexanes providing the pure tricyclic **3.52** as a white solid (7.6 g, 70%). Analytical data: 1.0:1.3 mixture of rotamers; R_f = 0.36 (10% EtOAc/hexanes); mp 83°-84°; $[\alpha]_D^{20}$ = -81.2 (*c* = 1.1, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (d, *J* = 11.2 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.64-6.60

(m, 1H, minor), 6.54-6.45 (m, 1H, major), 5.19-5.10 (m, 1H, minor), 5.08-4.96 (m, 1H, major), 4.61 (ddd, J = 14.8, 10.1, 4.8 Hz, 1H), 4.56-4.48 (m, 1H, minor), 4.33 (d, J = 8.8 Hz, 1H, minor), 4.25 (d, J = 9.8 Hz, 1H, major), 4.24-4.10 (m, 2H), 3.83 (dd, J = 9.8, 9.8 Hz, 1H, minor), 1.57 (s, 9H, minor), 1.50 (s, 9H, major); 125 MHz ^{13}C NMR ($CDCl_3$) δ 155.4 (major), 155.0 (minor), 151.8, 132.1 (minor), 131.9 (major), 130.9 (minor), 130.8 (major), 130.1 (major), 129.8 (minor), 127.1 (major), 126.4 (minor), 122.0 (major), 119.8 (minor), 114.5, 111.5 (minor), 111.2 (major), 87.7 (minor), 81.7 (major), 65.6 (major), 56.3 (major), 55.4 (major), 44.0 (minor), 42.0 (major), 28.9; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.9; CH_2 δ 65.9 (major), 65.5 (minor); CH δ 132.4 (minor), 132.3 (major), 131.2, 130.0 (major), 130.2 (minor), 120.3 (major), 120.1 (minor), 111.8 (minor), 111.6 (major), 56.6 (major), 55.8 (minor), 43.4 (minor), 42.3 (major); CH_0 δ 155.4 (major), 155.0 (minor), 151.8, 127.1 (major), 126.4 (minor), 114.5, 87.7 (minor), 81.6 (major); IR (neat) 2975, 2933, 2875, 1704, 1482, 1384, 1256, 1232, 1167, 1136, 1082 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}NO_3NaBr$ (M+Na): 374.0368, found: 374.0370; Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.28; H, 5.13; N, 3.86.



(3a*S*,9b*S*)- tert-butyl-8- bromo-1,3a,4,9b- tetrahydrochromeno[3,4-b] pyrrole-3(2H)-carboxylate (3.53). To a stirring solution of enamine **3.52** (1.02 g, 2.90 mmol, 1.0 equiv) in acetone (30 mL) in a 50 mL 3 -necked rb flask, was added platinum oxide (33 mg, 0.15 mmol, 0.05 equiv). The reaction flask was equipped with a hydrogen balloon. After 6 h at rt, the reaction mixture was filtered over a pad of Celite, and then washed with

copious amounts of acetone. Purification was accomplished by flash column chromatography eluting with 10% EtOAc/hexanes providing reduced product **3.53** (0.98 g, 96 %) as a white solid: Analytical data: 1.0:1.3 mixture of rotamers; R_f = 0.22 (10 % EtOAc/hexanes); mp 109°-110°; $[\alpha]_D^{20}$ = -160.0 (*c* = 1.1, $CDCl_3$);); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.29 (s,1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.41-4.28 (m, 1H), 4.19-4.11 (m, 1H, minor), 4.09-4.01 (m, 1H, major), 3.72 (ddd, *J* = 10.3, 10.3, 10.3 Hz, 1H, minor), 3.57 (ddd, *J* = 9.8, 9.8, 9.8 Hz, 1H, major), 3.50-3.28 (m, 3H), 2.46-2.33 (m, 1H), 1.90 (dddd, *J* = 18.3, 9.1, 9.1, 9.1 Hz, 1H), 1.51 (s, 9H, major), 1.49 (s, 9H, minor); 125 MHz ^{13}C NMR ($CDCl_3$) δ 154.6 (minor), 154.4 (major), 154.0 (minor), 153.6 (major), 132.2 (major), 132.1 (minor), 130.7 (major), 130.6 (minor), 126.7 (minor), 126.6 (major), 119.1 (minor), 119.0 (major), 113.5 (major), 113.4 (minor), 80.2 (major), 79.9 (minor), 65.2 (major), 65.0 (minor), 53.2 (minor), 52.9 (major), 45.5 (minor), 45.1 (major), 38.0 (major), 37.1 (minor), 33.3 (minor), 32.3 (major), 28.7; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 28.7; CH_2 δ 65.3 (major), 65.1 (minor), 45.6 (minor), 45.2 (major), 33.3 (minor), 32.4 (major); CH δ 132.3 (major), 132.2 (minor), 130.8 (major), 130.7 (minor), 119.2 (minor), 119.1 (major), 53.3 (minor), 53.0 (major), 38.0 (major), 37.2 (minor); CH_0 δ 154.6 (minor), 154.4 (major), 154.0 (minor), 153.6 (major), 126.7 (minor),126.6 (major), 113.5 (major), 113.4 (minor), 80.2 (major), 79.9 (minor); IR (neat) 2975, 2878, 1695, 1482, 1397, 1255, 1233, 1173, 1125, 1031 cm^{-1}; Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.25; H, 5.69; N, 3.95. Found: C, 54.54; H, 5.76; N, 3.88.



(3a*S*,9b*S*)-8-bromo-1,2,3,3a,4,9b-hexahydro chromeno[3,4-b]pyrrole (3.54). To a stirring solution of carbamate **3.53** (178 mg, 0.51 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) in a 25 mL rb flask at 0 °C, was added trifluoroacetic acid (0.19 mL, 2.53 mmol, 5.0 equiv) dropwise. TLC analysis after stirring at rt for 6 h indicated complete consumption of the starting material. The reaction mixture was quenched by the slow addition of saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with 10% MeOH/CH_2Cl_2 providing deprotected product **3.54** (120 mg, 94%) as a white solid. Analytical data: R_f = 0.37 (10 % MeOH/ CH_2Cl_2); mp 55°-56°; $[\alpha]_D^{20}$ = -153.8 (*c* = 1.1, $CDCl_3$);); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (dd, *J* = 2.4, 1.0 Hz, 1H), 7.20 (dd, *J* = 9.3, 2.5 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 4.03 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.88 (dd, *J* = 11.2, 6.3 Hz, 1H), 3.60-3.50 (m, 1H), 3.33 (ddd, *J* = 7.3 7.3, 7.3 Hz, 1H), 3.09-2.95 (m, 2H), 2.41 (dddd, *J* = 12.7, 7.8, 7.8, 4.9 Hz, 1H), 1.93 (br s, 1H), 1.83 (dddd, *J* = 12.7, 7.3, 7.3, 7.3 Hz, 1H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 154.1, 132.9, 130.5, 129.1, 119.4, 113.9, 67.9, 55.5, 46.1, 38.7, 35.6; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_2 δ 67.9, 46.1, 35.6; CH δ 132.9, 130.5, 119.4, 55.5, 38.7; CH_0 δ 154.1, 129.1, 113.9; IR (neat) 2957, 2916, 2871, 1644, 1555, 1480, 1405, 1253, 1227, 1025, 815 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}NO_3NaBr$ (M+Na): 254.0181, found: 254.0190; Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 51.99; H, 4.76; N, 5.51. Found: C, 51.87; H, 4.66; N, 5.42.

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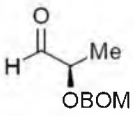
APPENDIX A

^{1}H, ^{13}C, AND DEPT SPECTRA FOR CHAPTER 1



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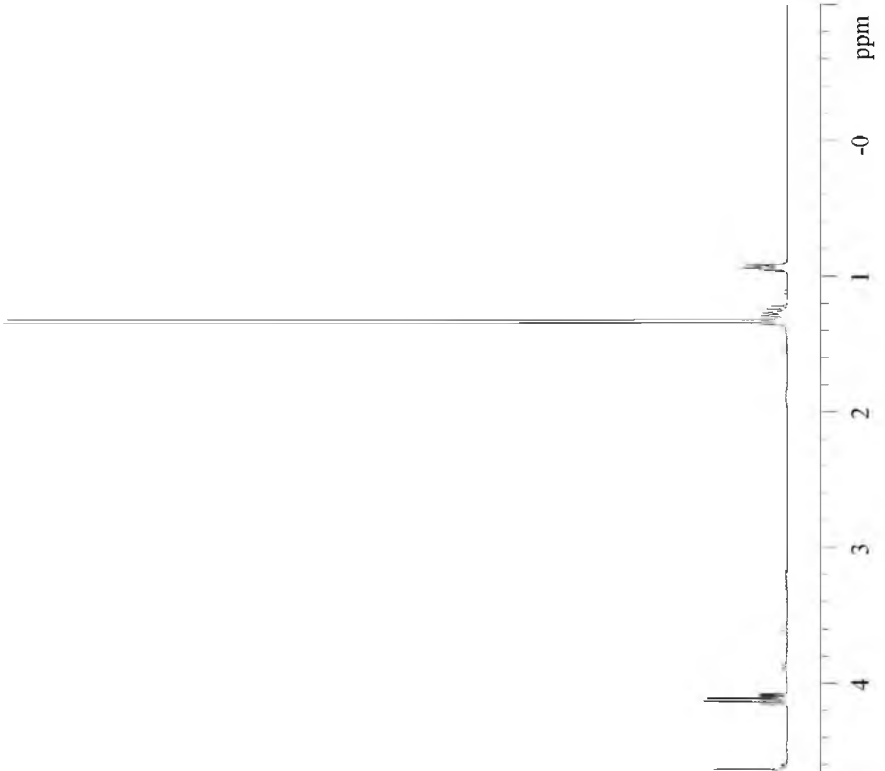
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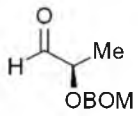

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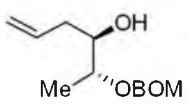

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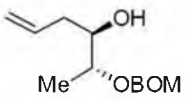

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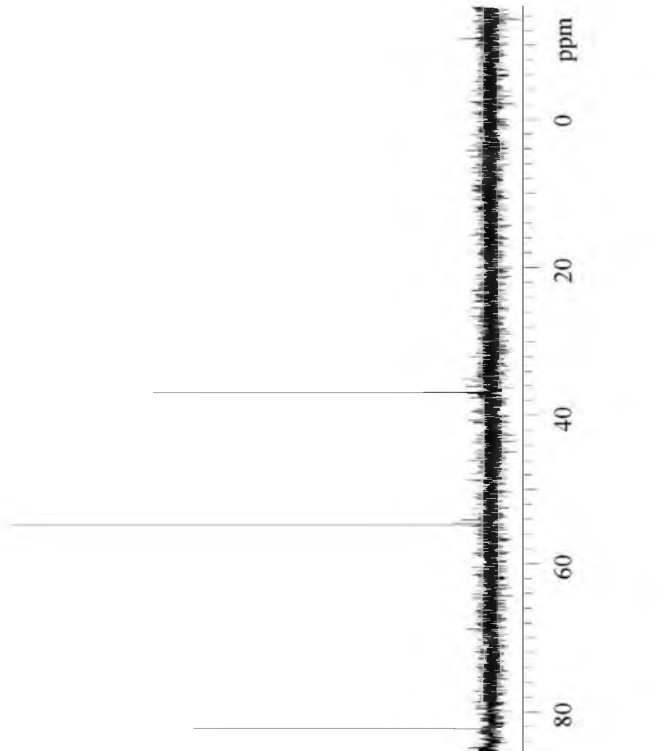
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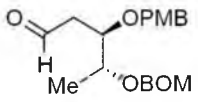

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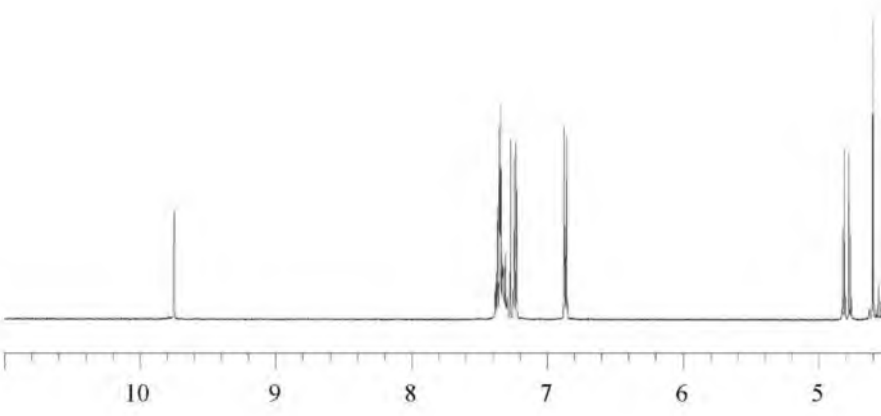


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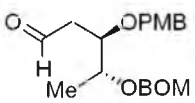

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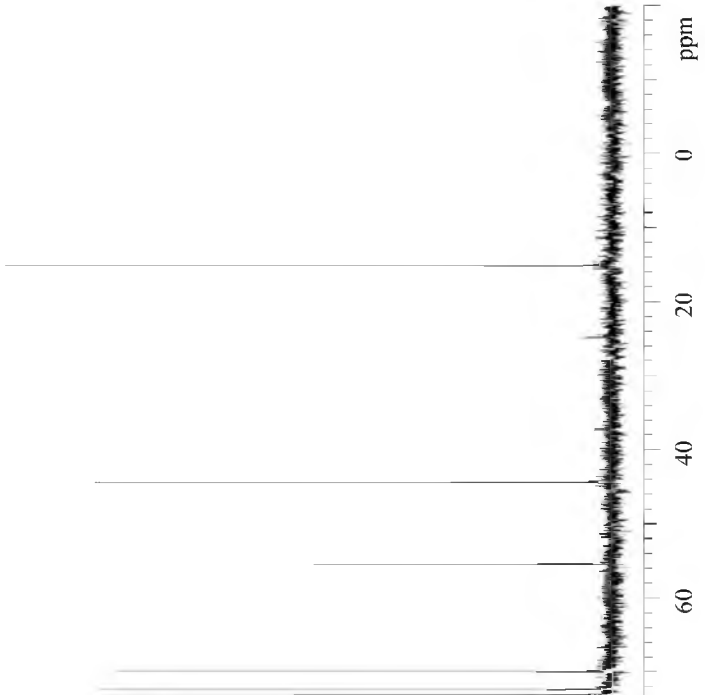
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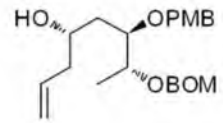

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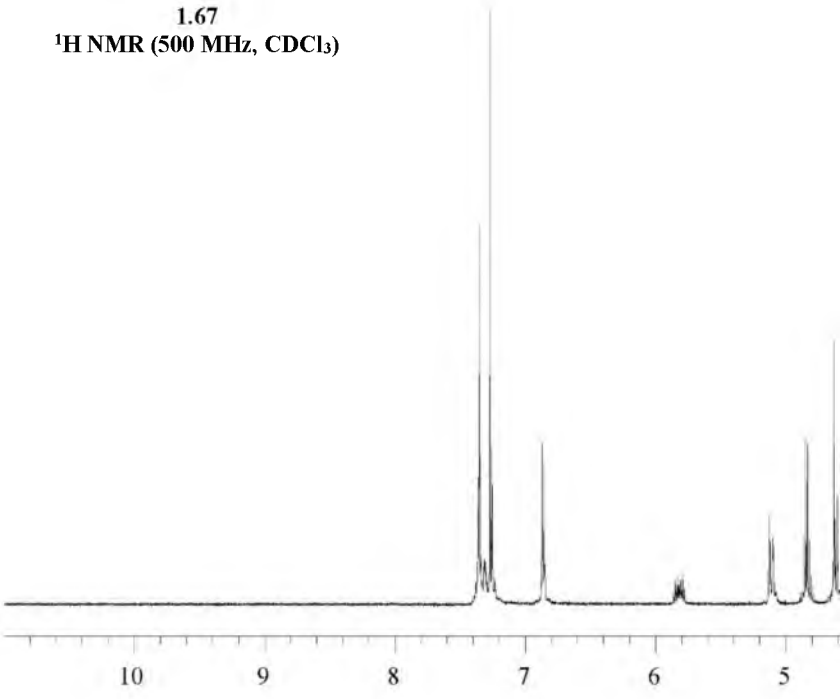

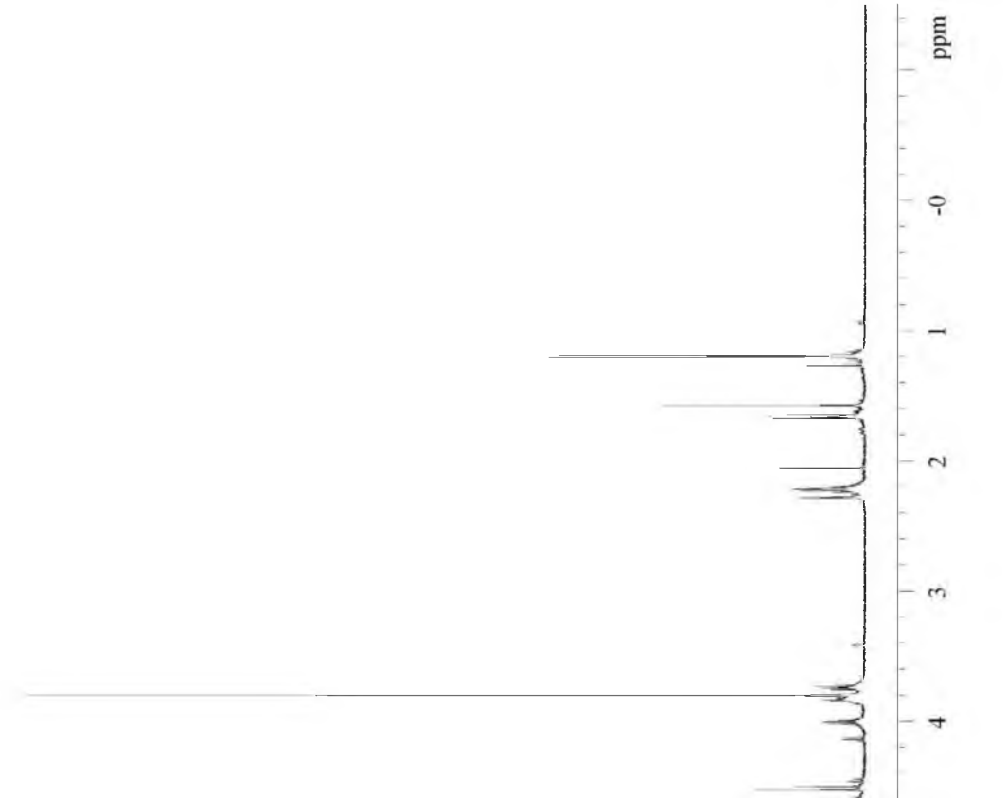
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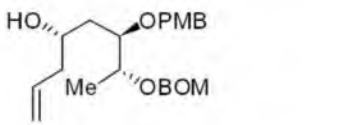

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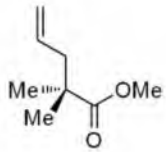

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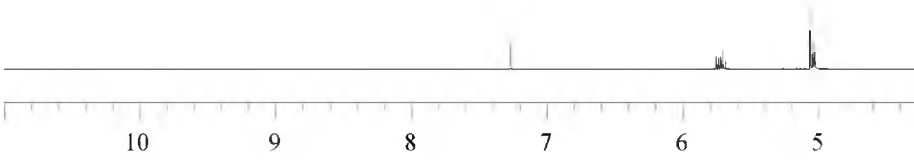

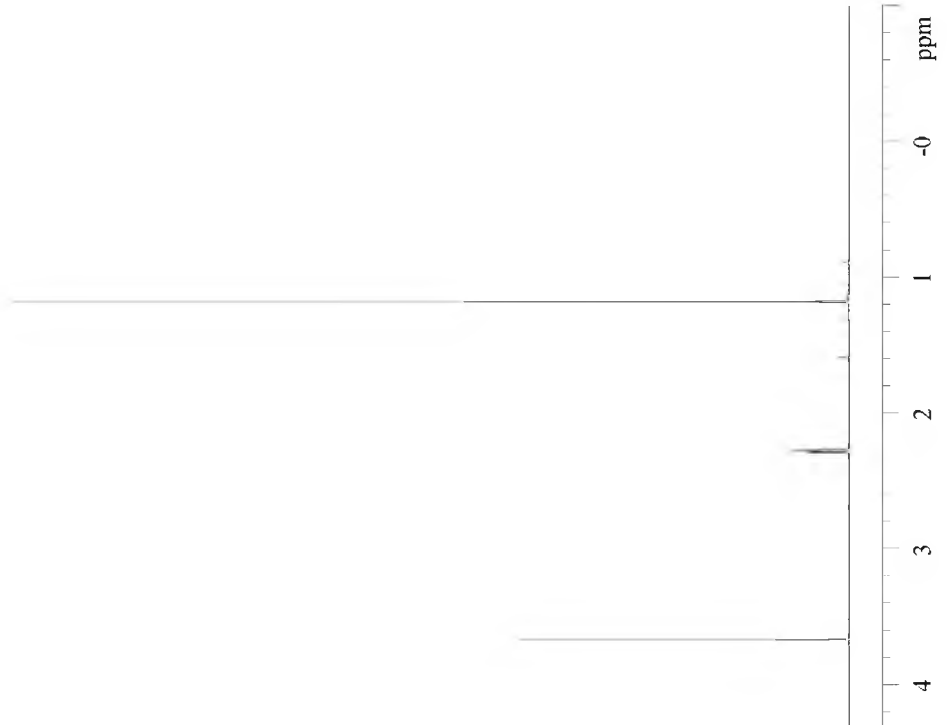
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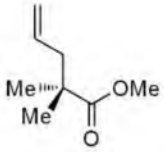

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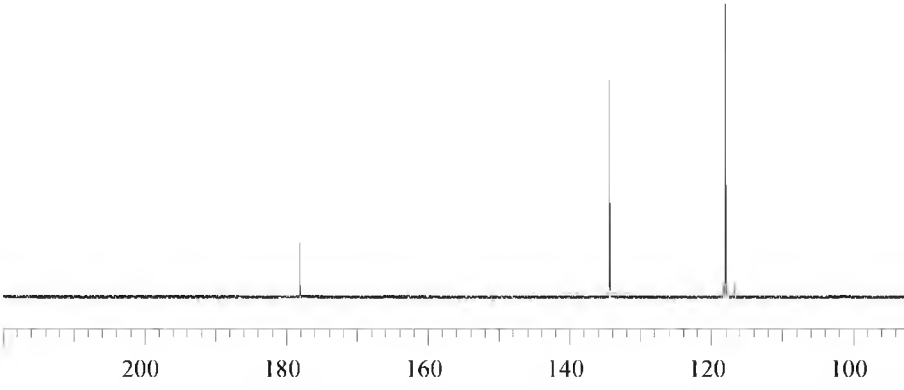

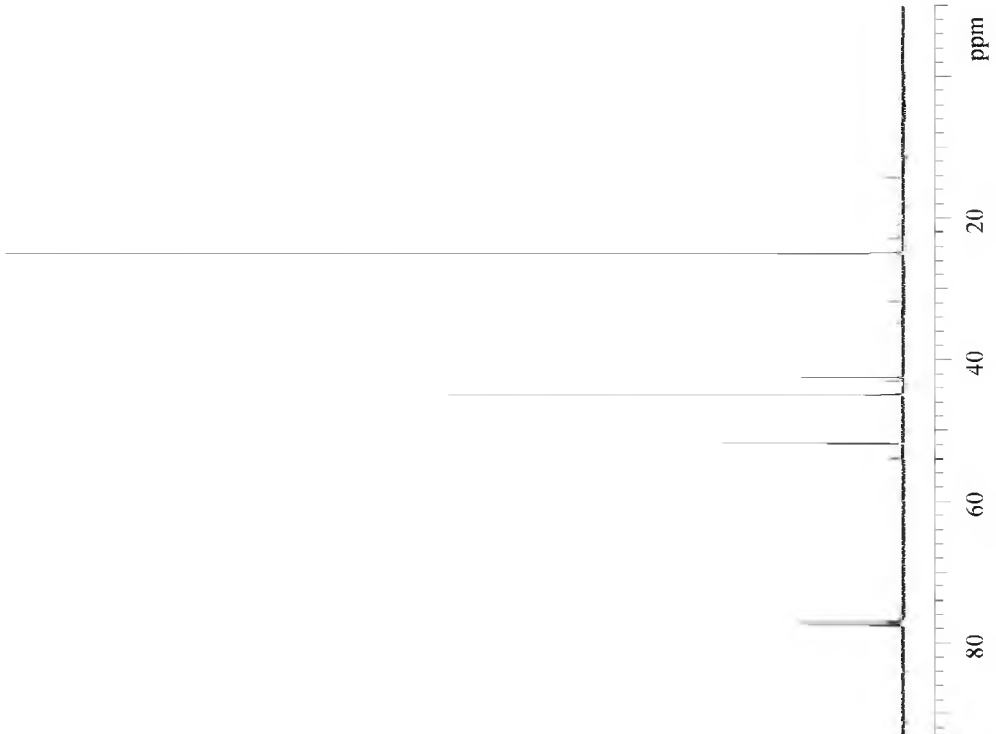
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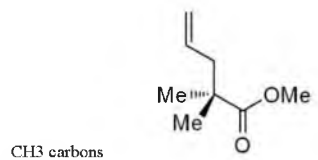

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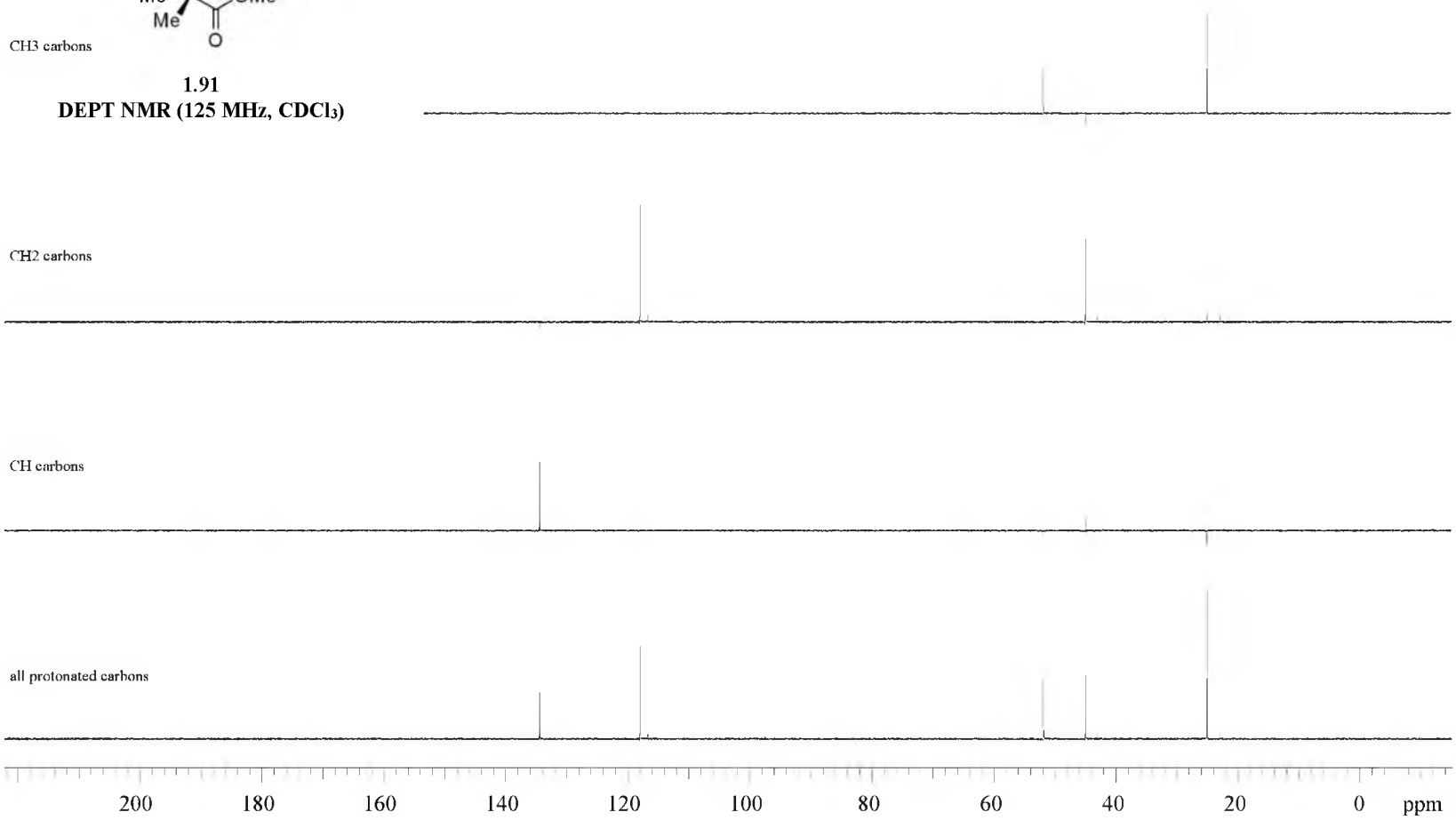

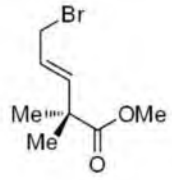

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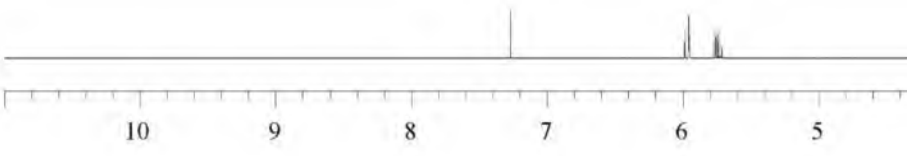

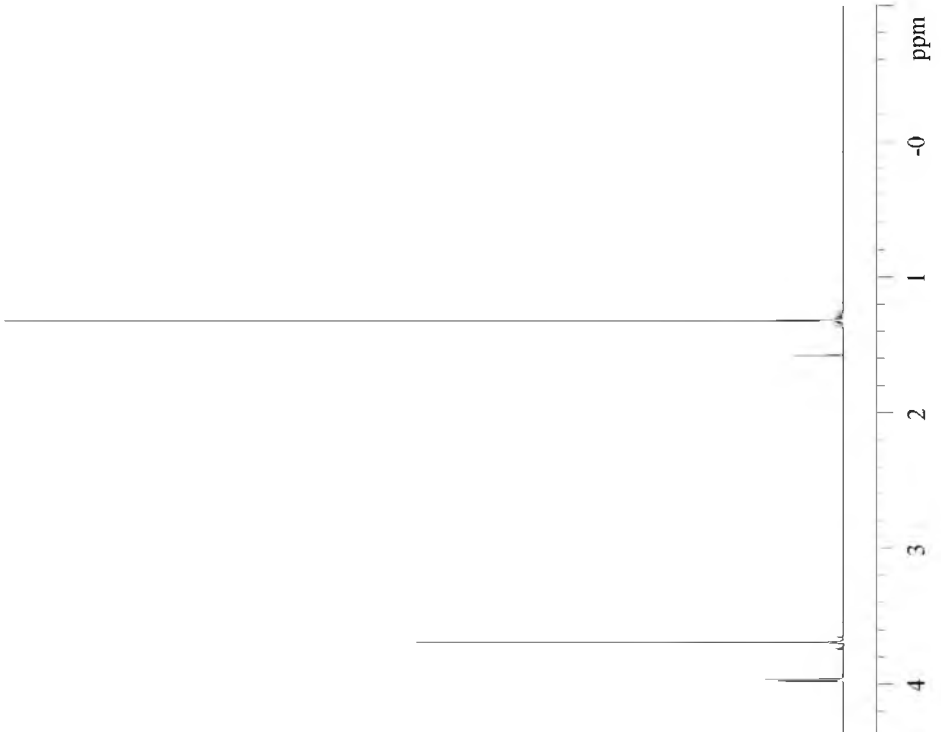
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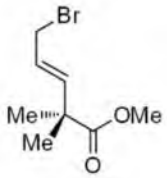

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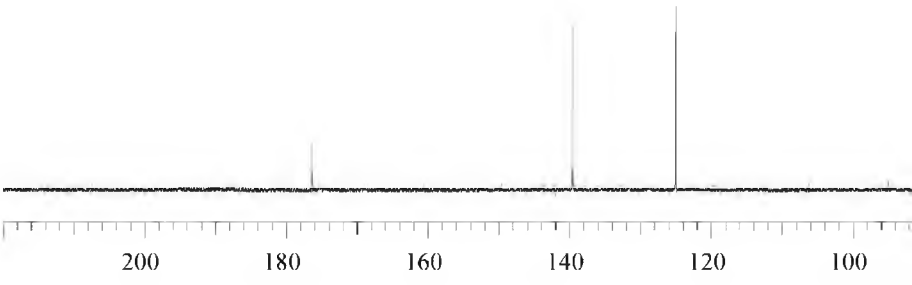

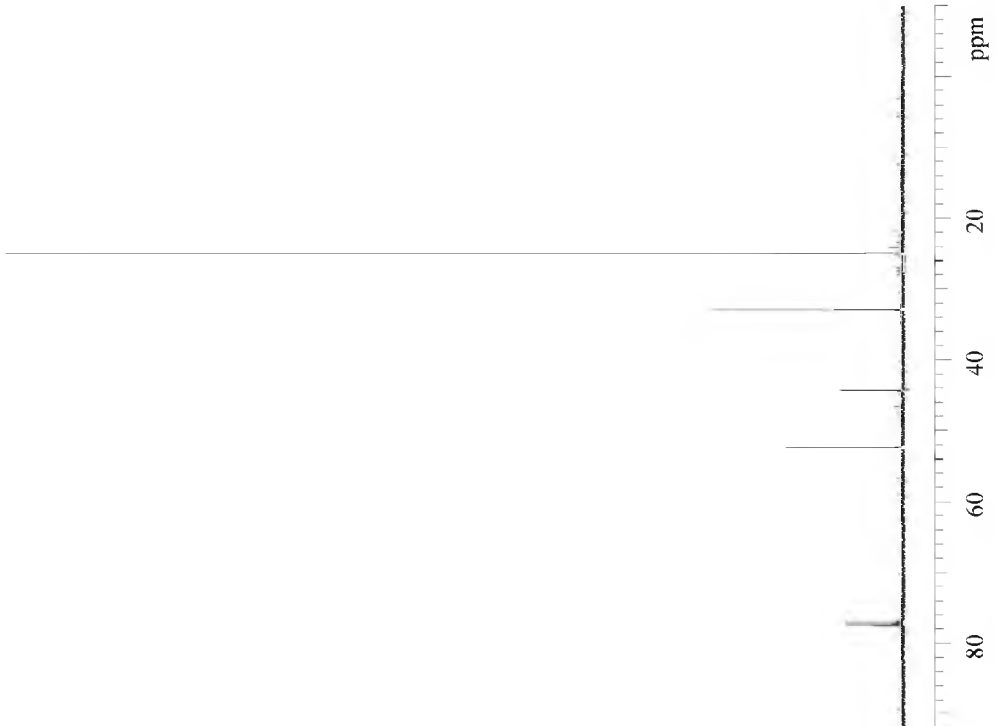
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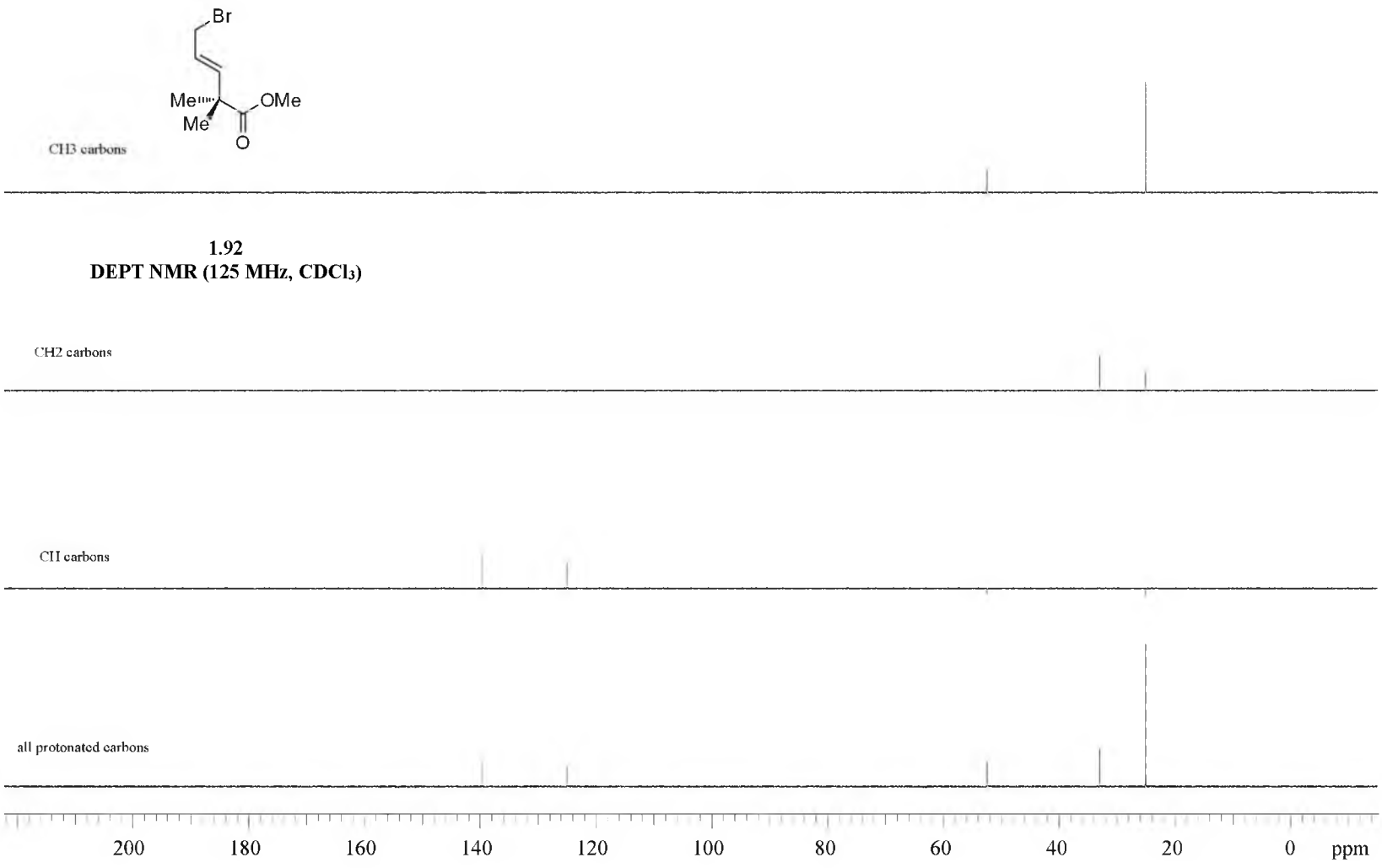

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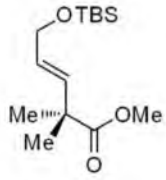
DEPT NMR (125 MHz, $CDCl_3$)



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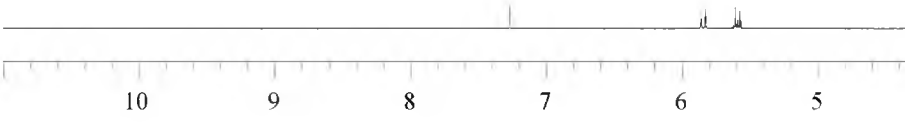


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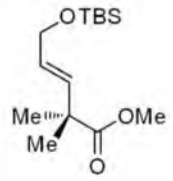
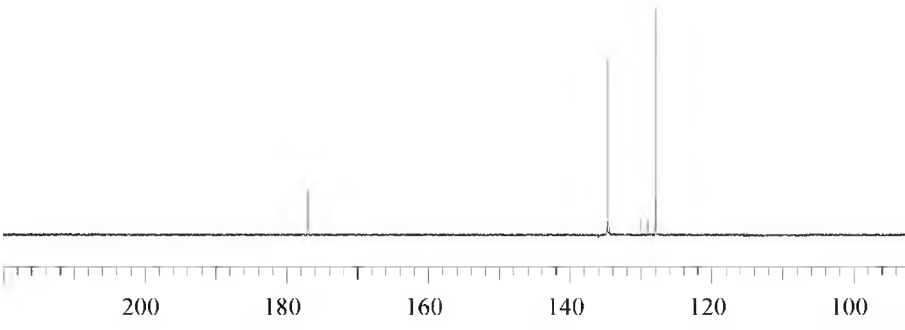
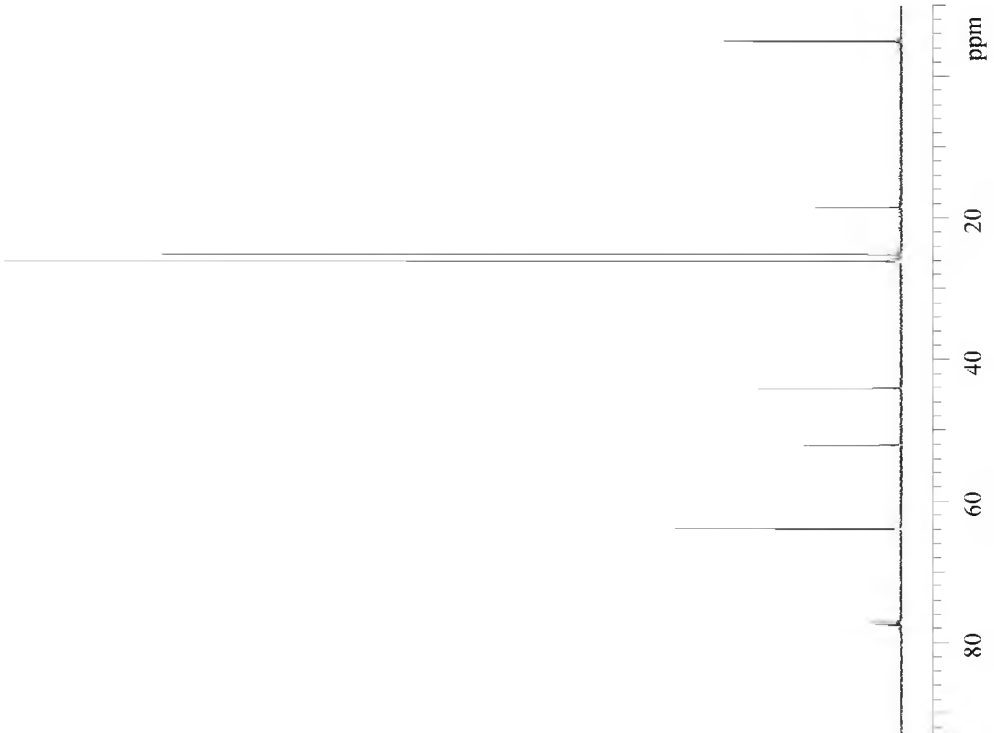


1.93
^{13}C NMR (125 MHz, $CDCl_3$)

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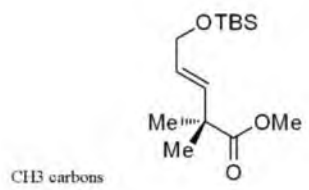
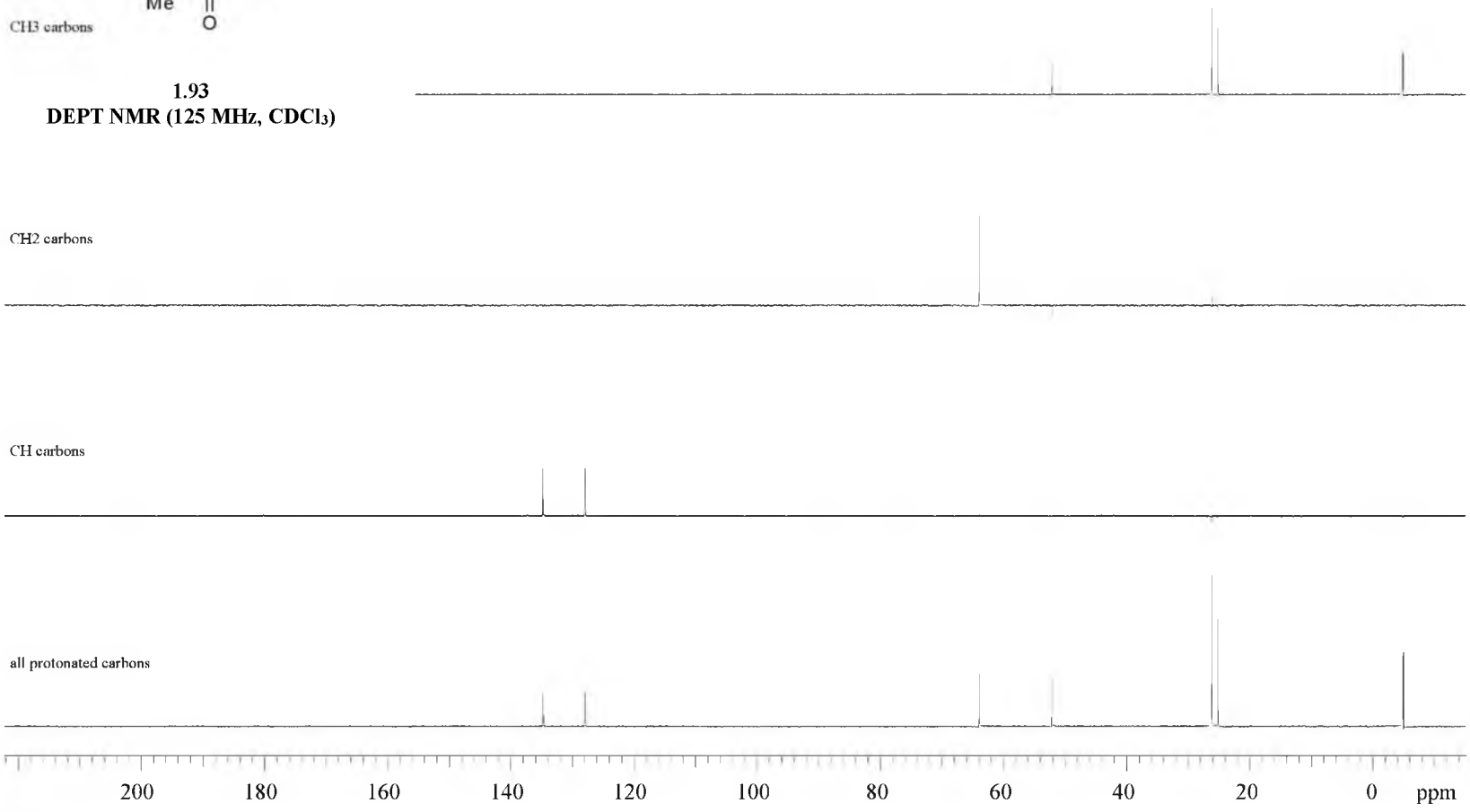
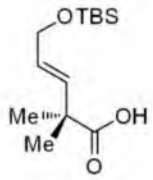
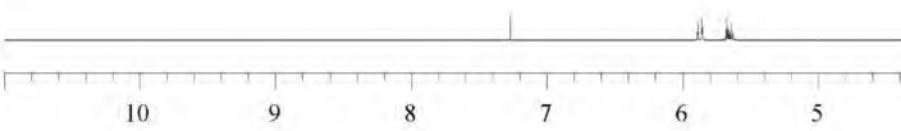


1.93
DEPT NMR (125 MHz, $CDCl_3$)





1.88
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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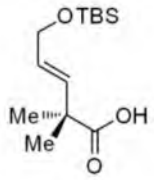
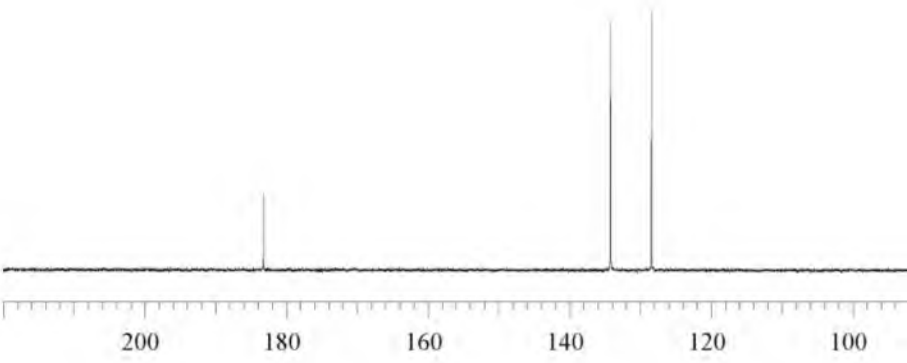
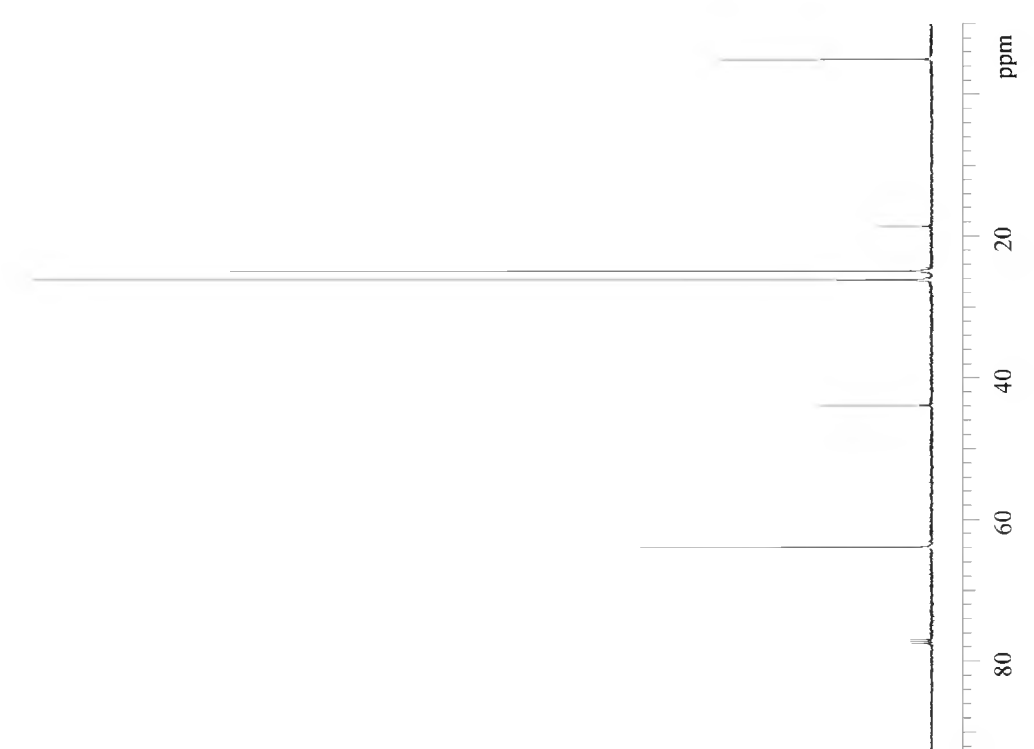


1.88
^{13}C NMR (125 MHz, $CDCl_3$)

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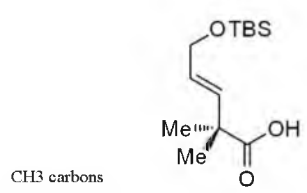
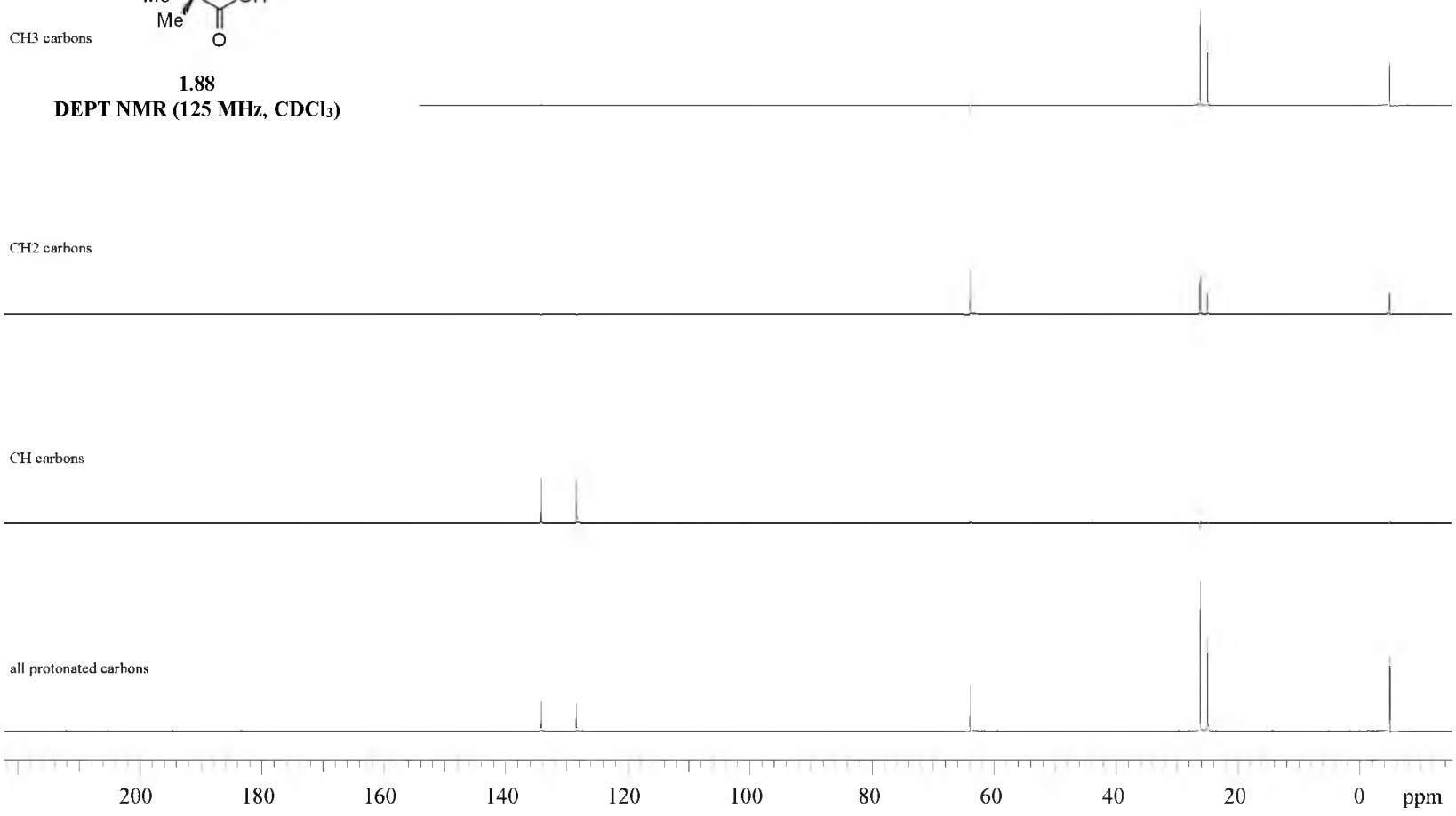
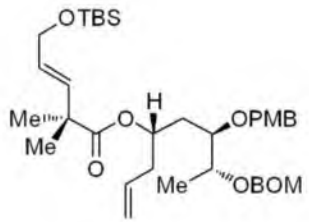
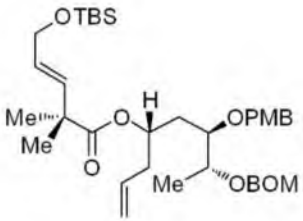


1.88
DEPT NMR (125 MHz, $CDCl_3$)

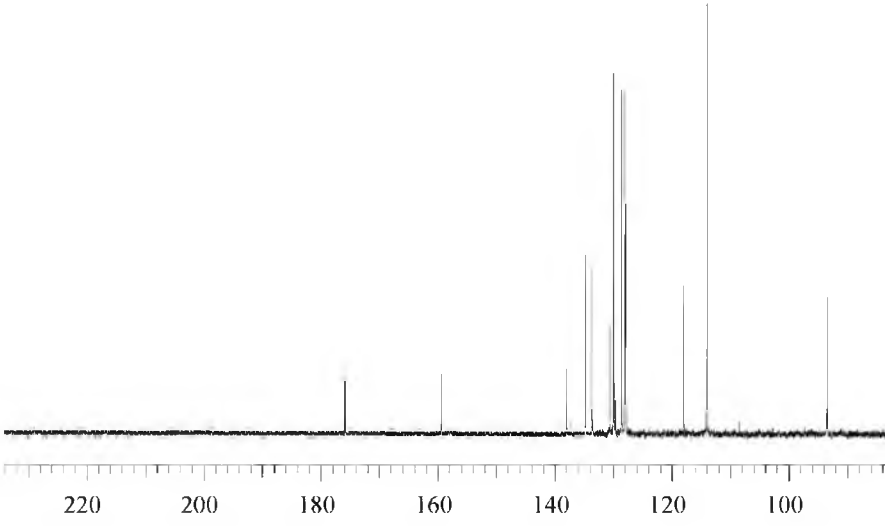


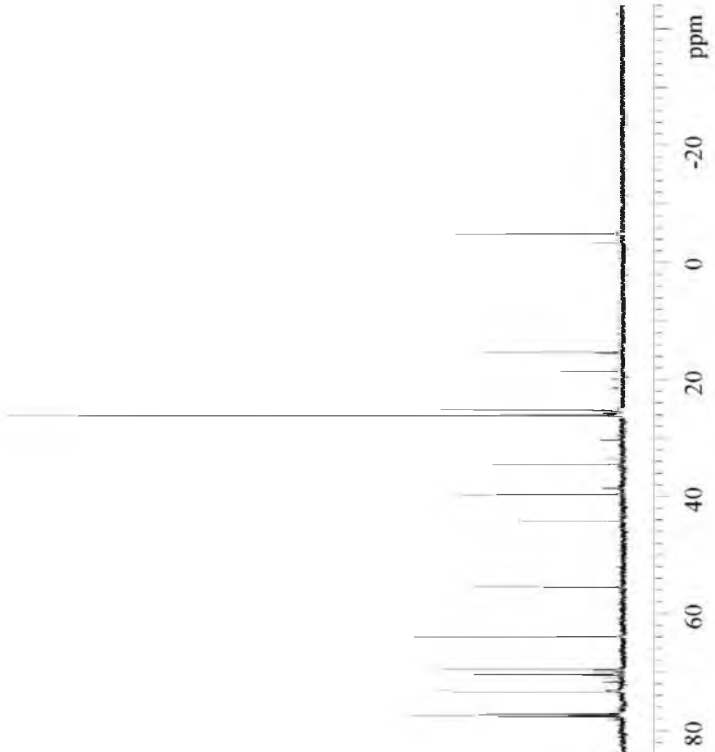


1.98
^{1}H NMR (500 MHz, $CDCl_3$)



1.98
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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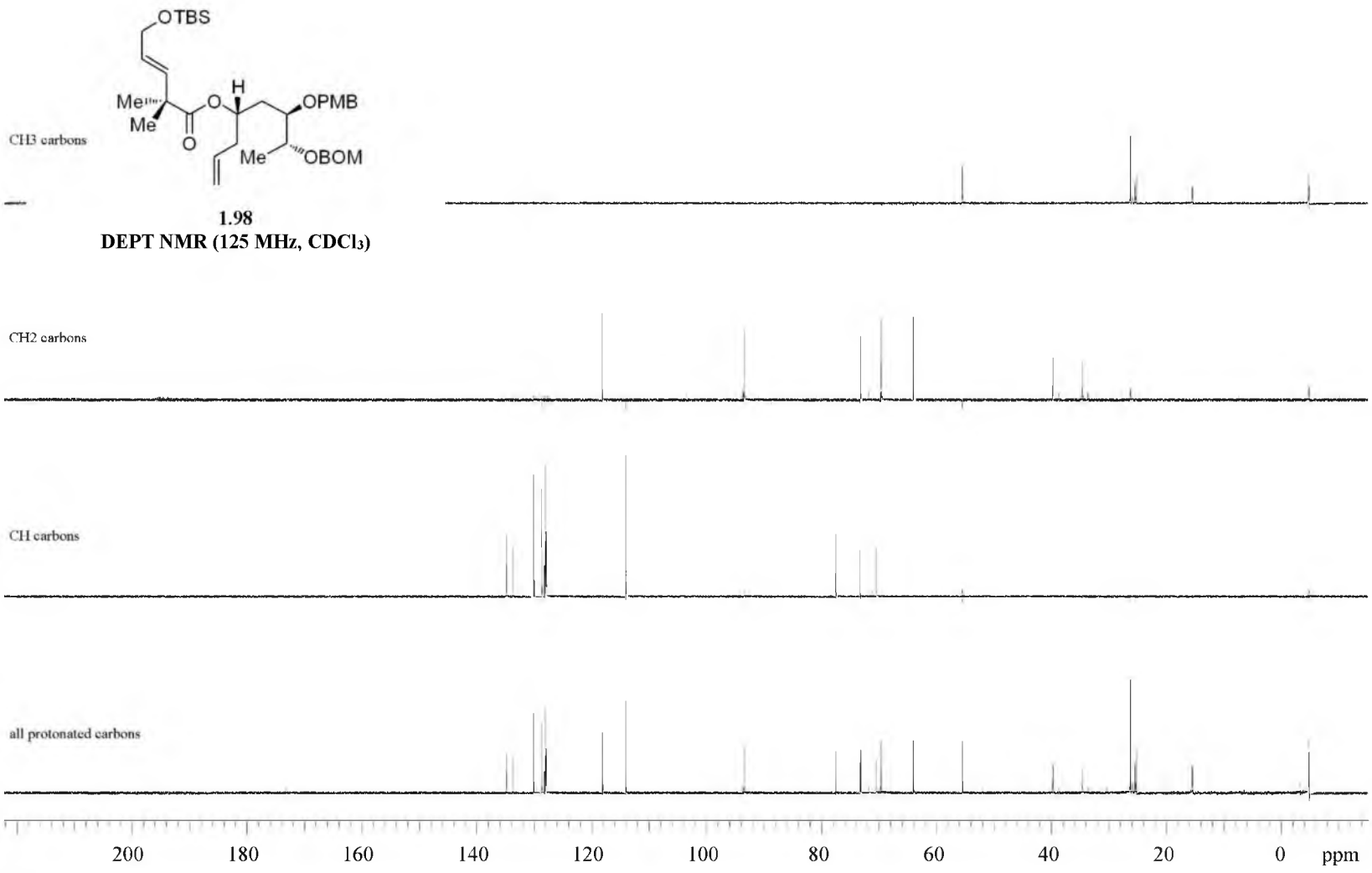
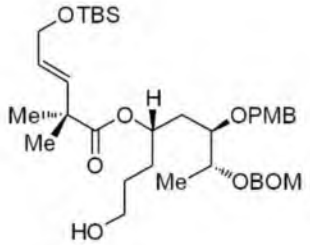
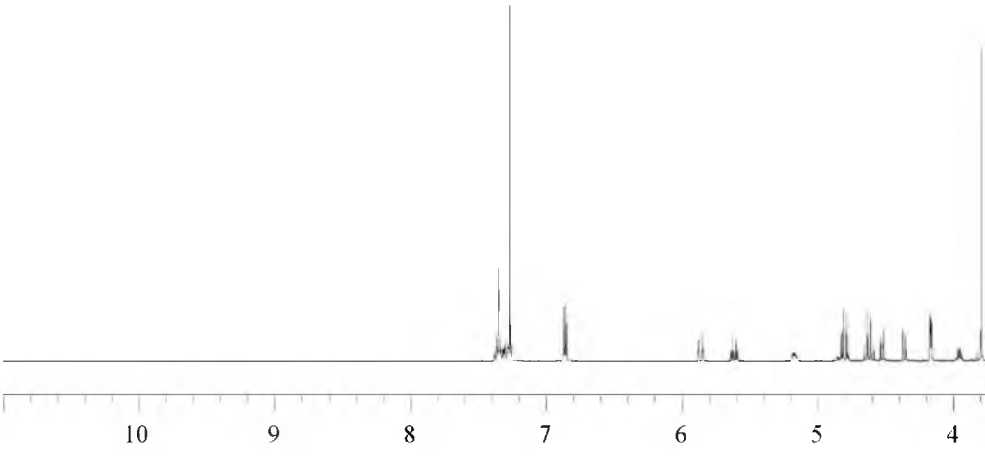


1.98
DEPT NMR (125 MHz, $CDCl_3$)



1.99
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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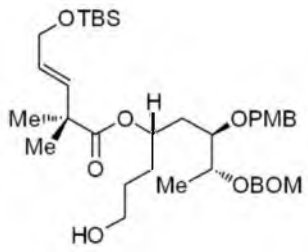
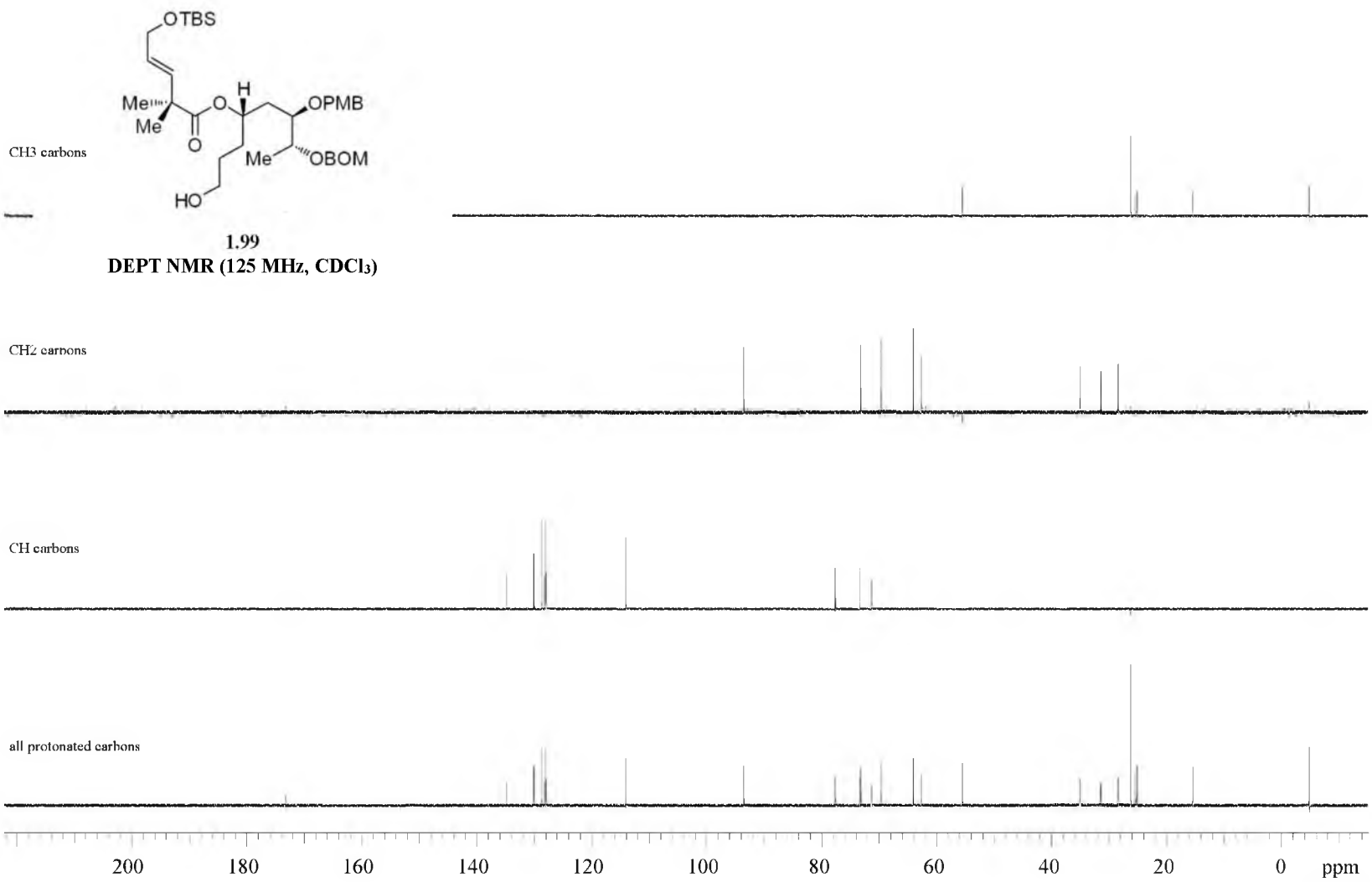
3

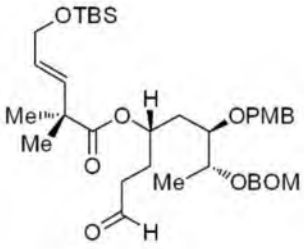


1.99
^{13}C NMR (125 MHz, $CDCl_3$)

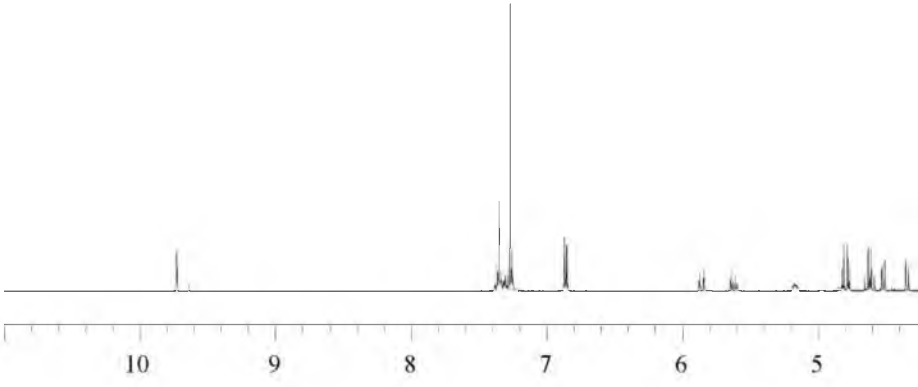


1.99

DEPT NMR (125 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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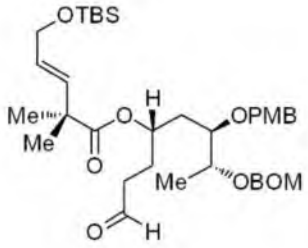
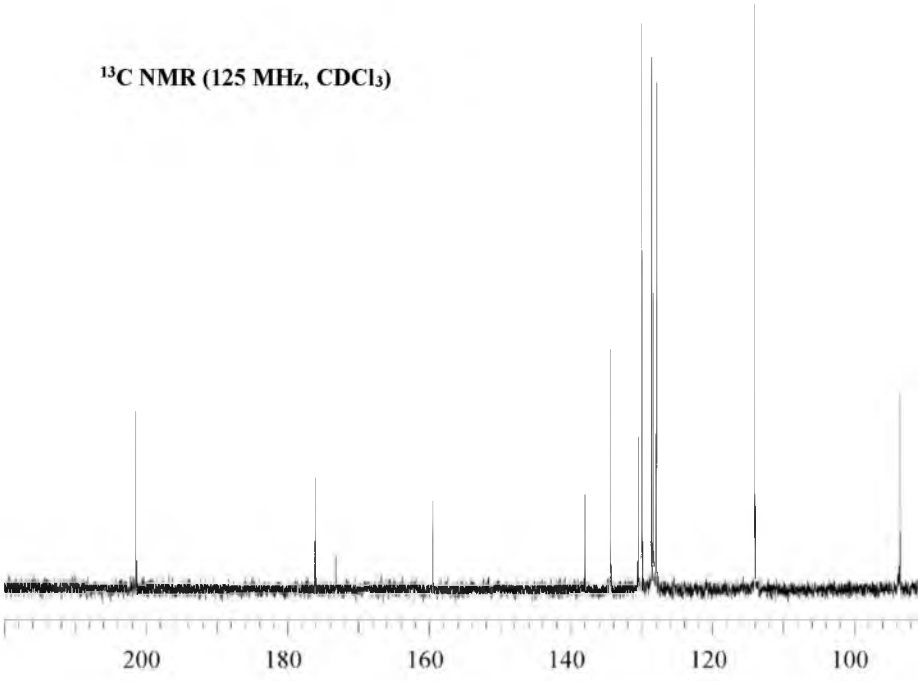
3
4



^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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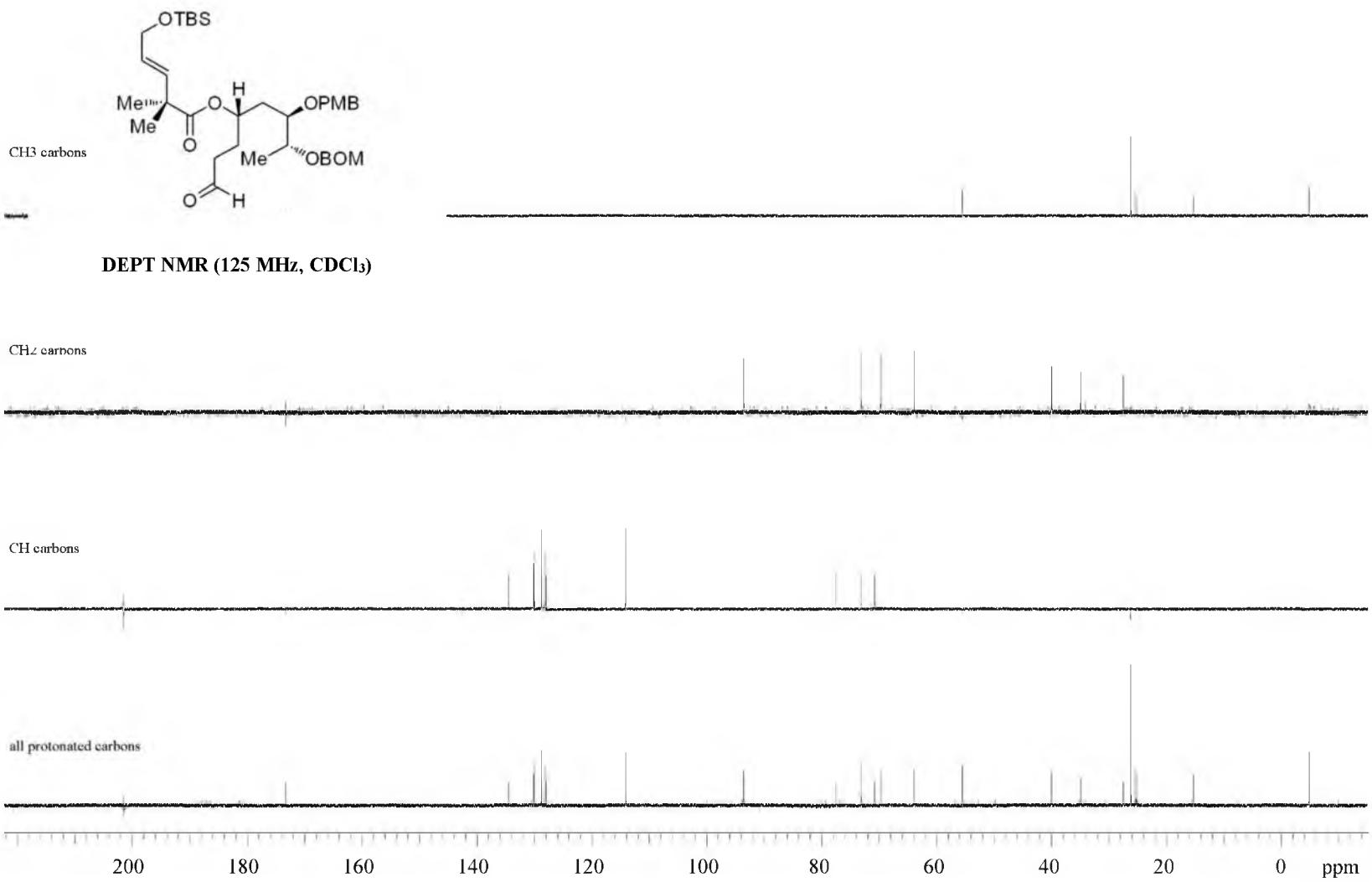
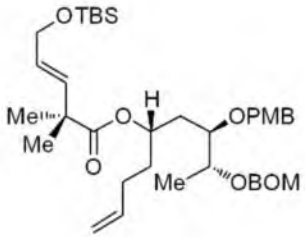
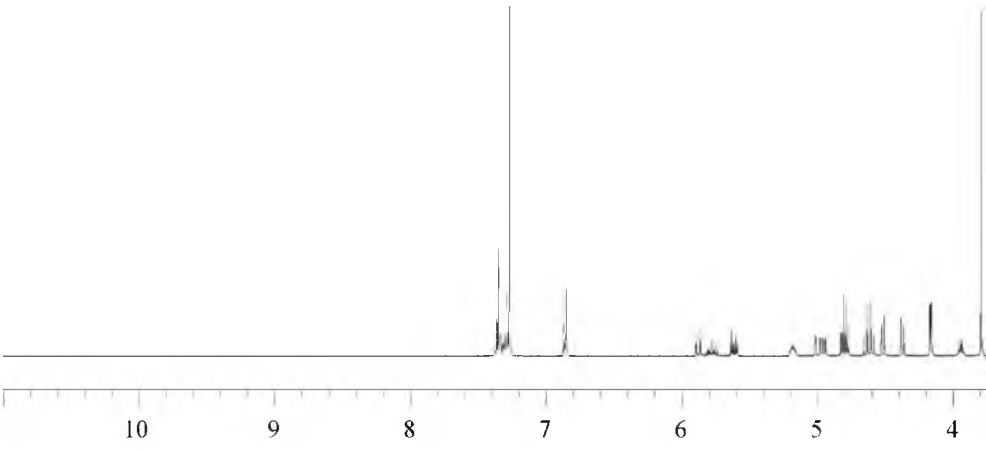


DEPT NMR (125 MHz, $CDCl_3$)



1.87
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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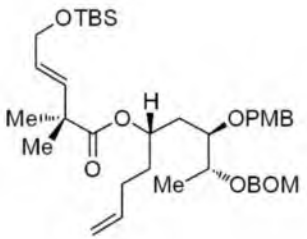
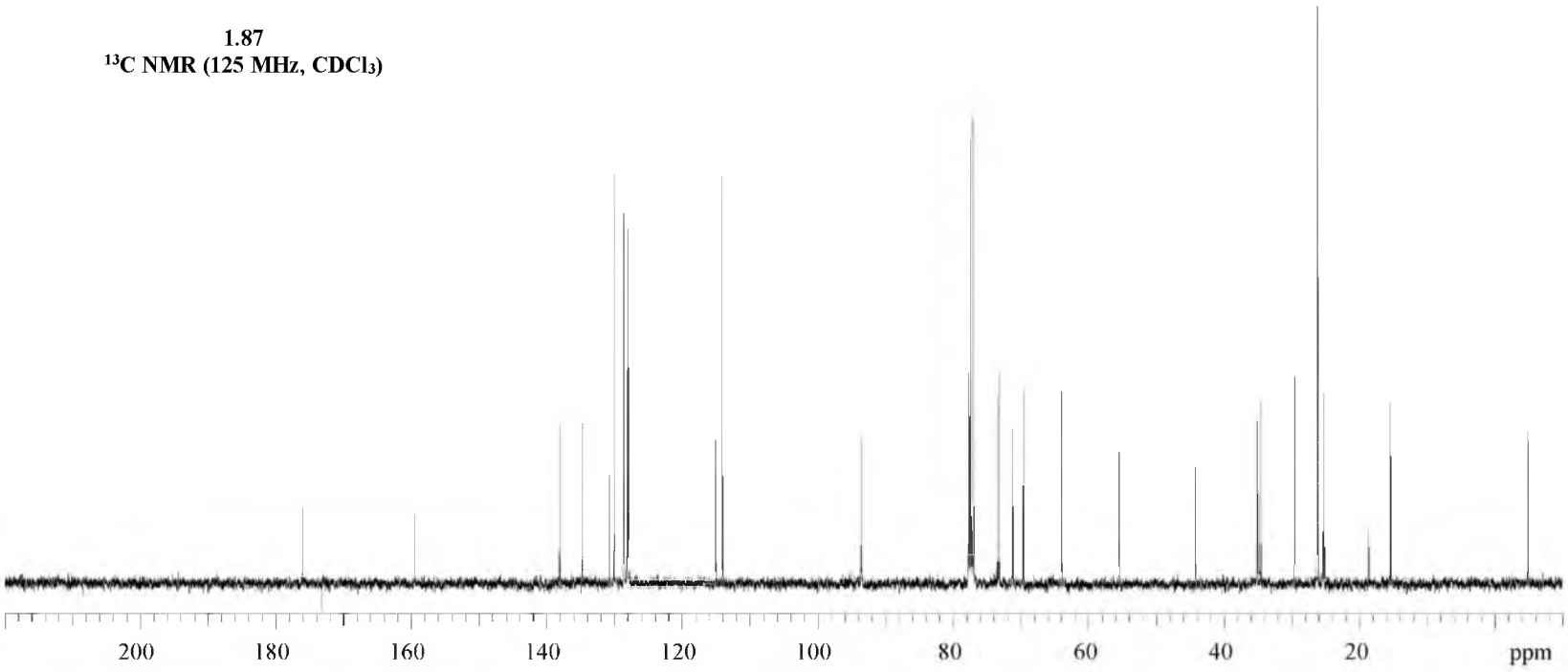
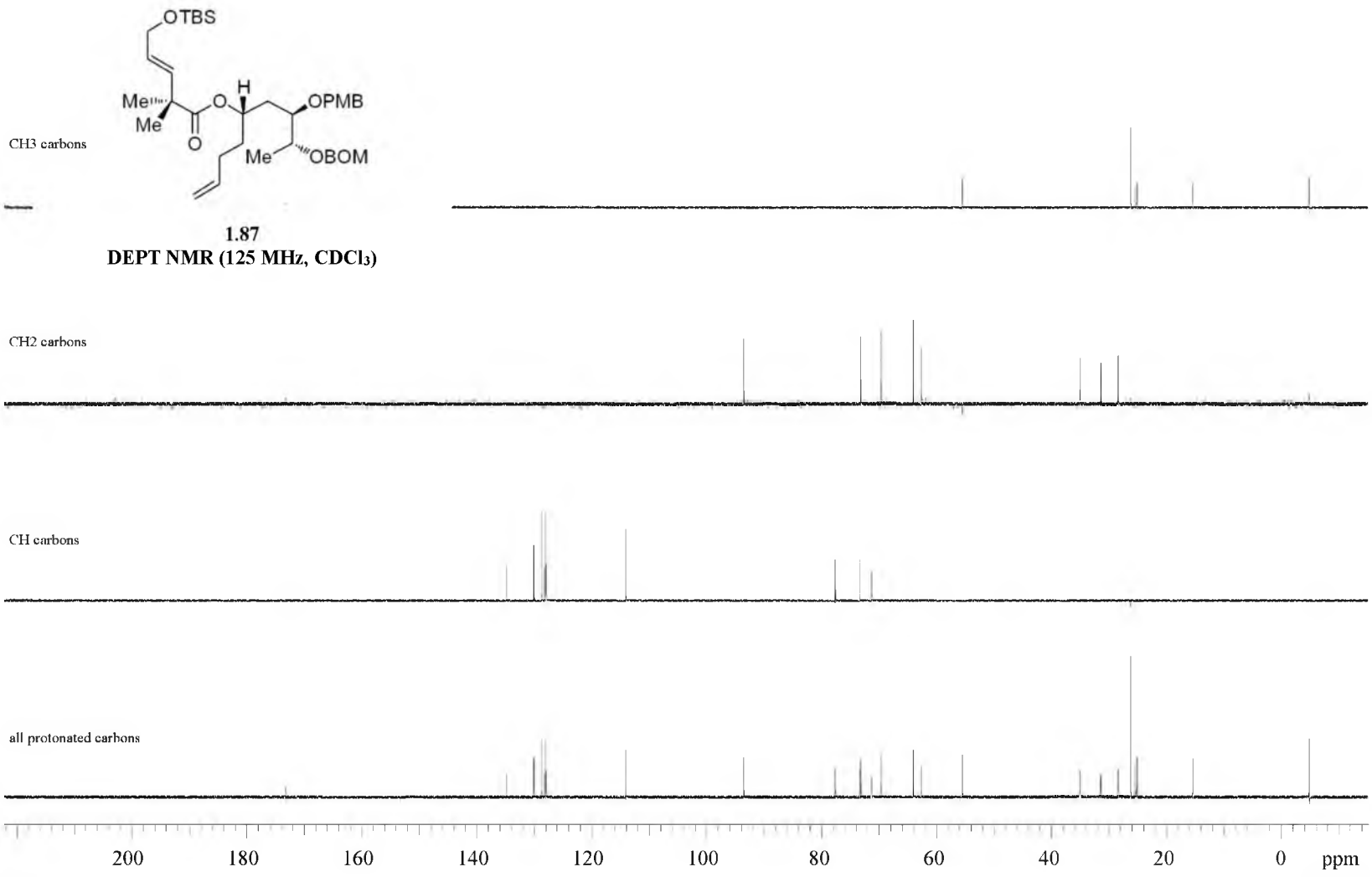


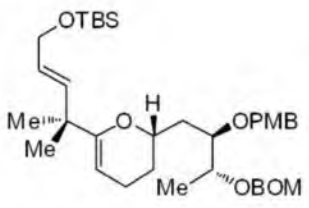
1.87
^{13}C NMR (125 MHz, $CDCl_3$)



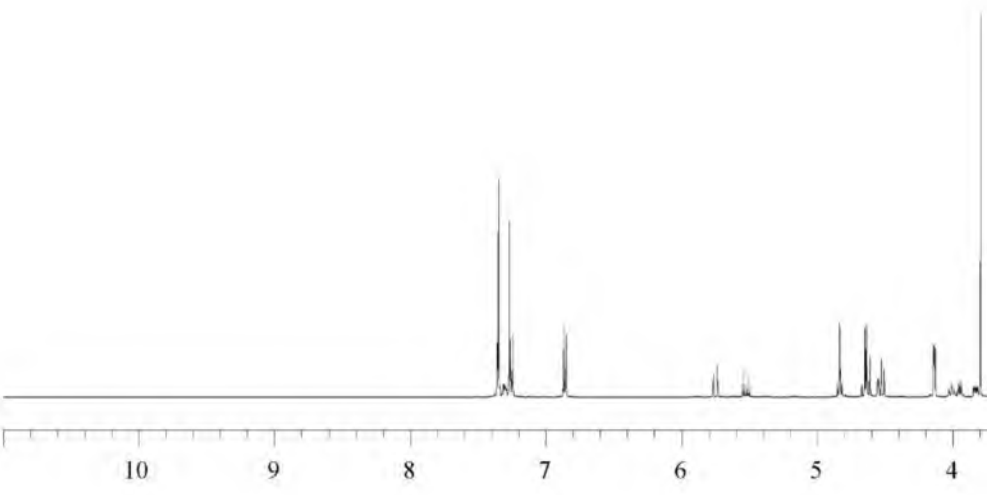


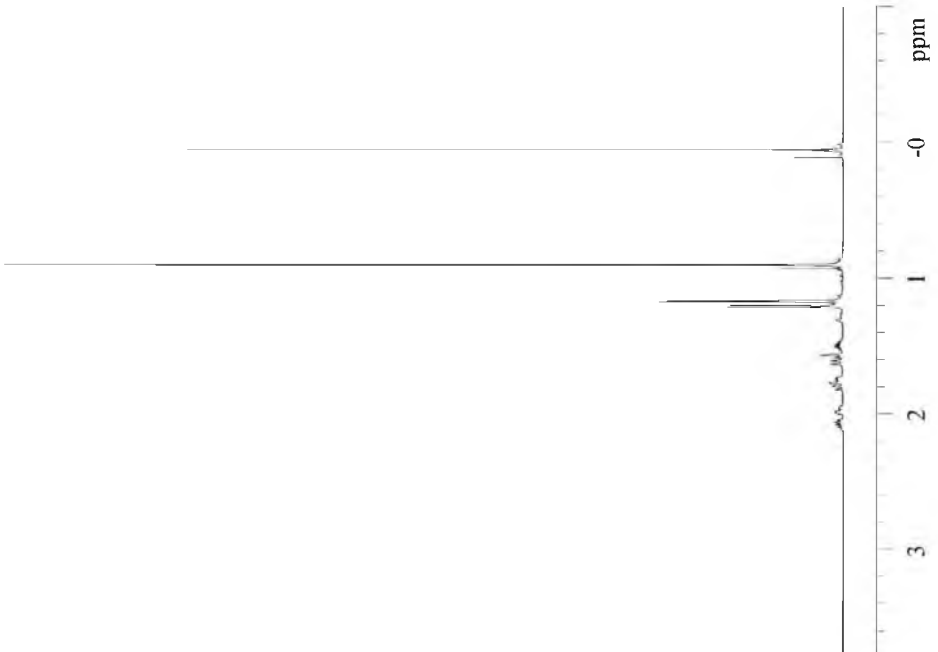
1.87

DEPT NMR (125 MHz, $CDCl_3$)



1.86
^{1}H NMR (500 MHz, $CDCl_3$)

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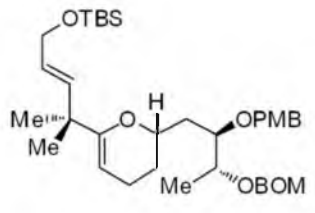
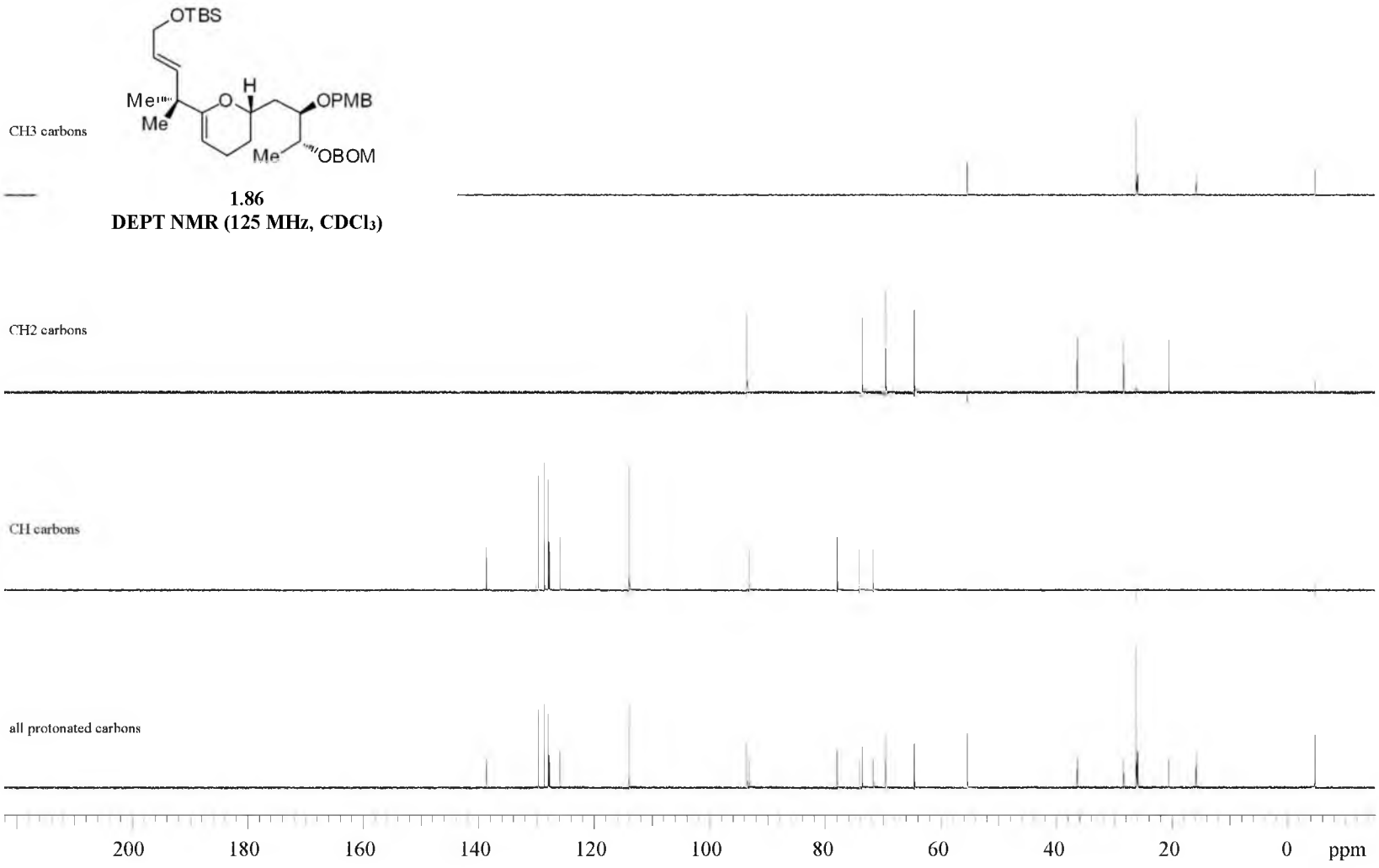
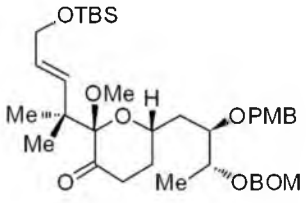
3



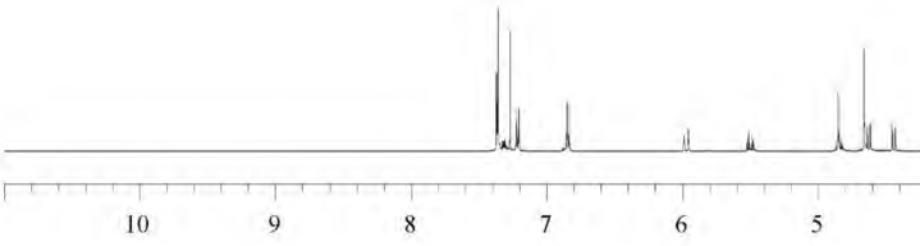
1.86
^{13}C NMR (125 MHz, $CDCl_3$)



1.86
DEPT NMR (125 MHz, $CDCl_3$)



1.85
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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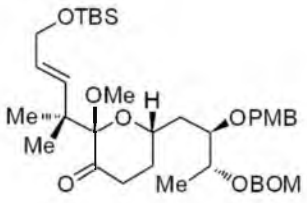
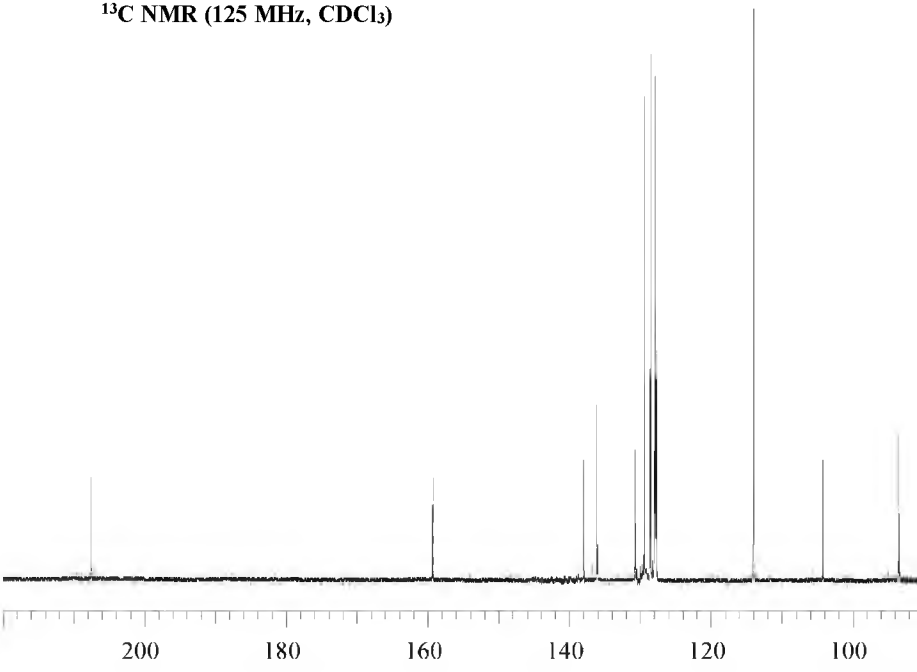
4



1.85

^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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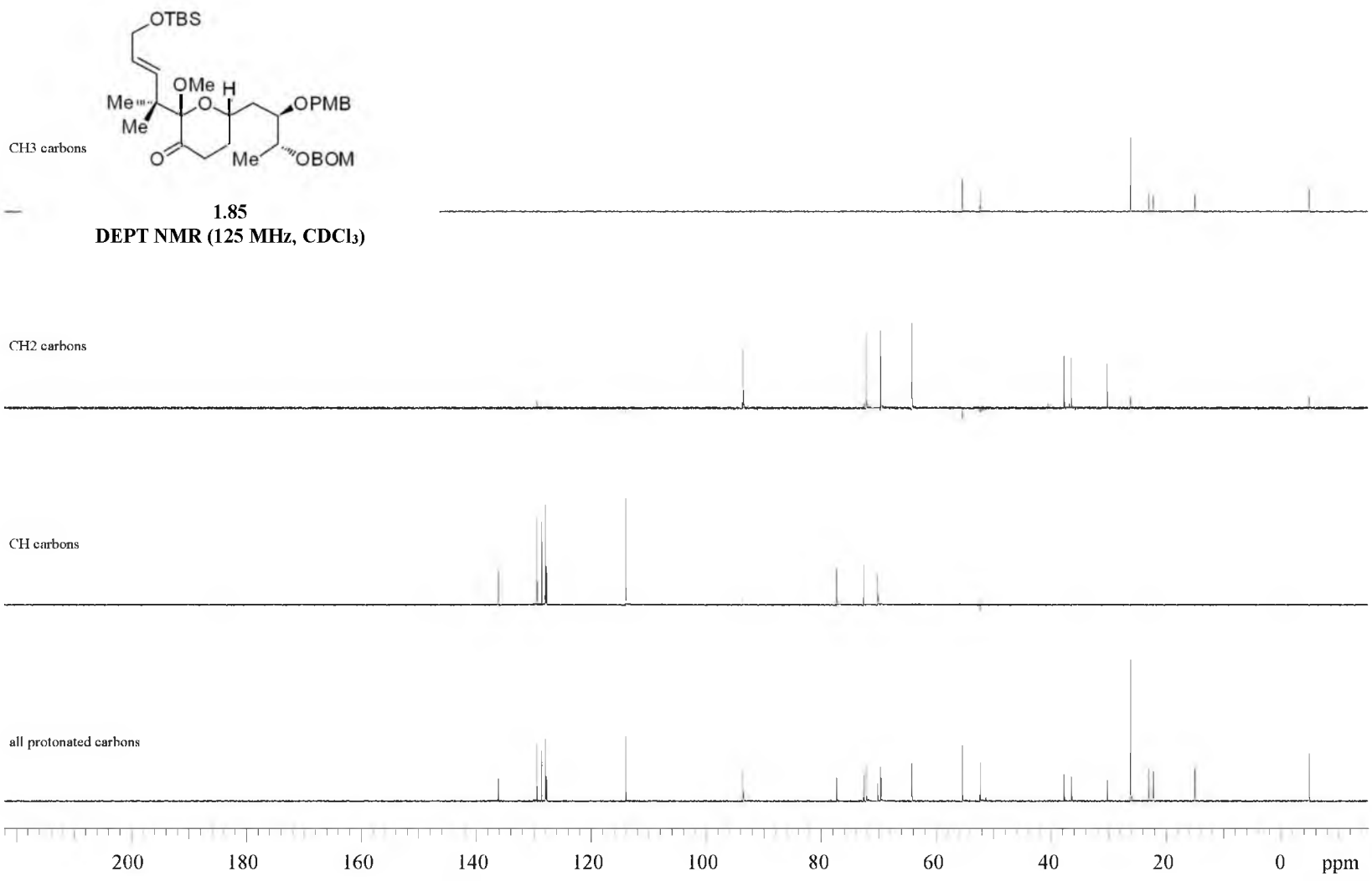
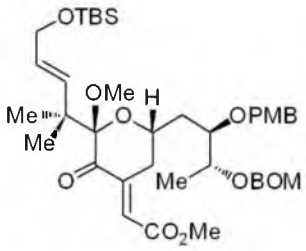
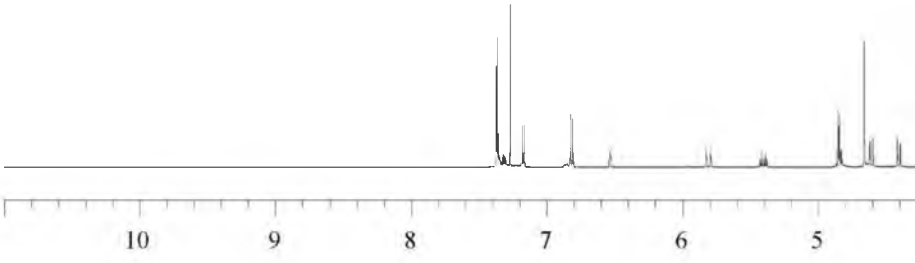


1.85
DEPT NMR (125 MHz, $CDCl_3$)



1.103
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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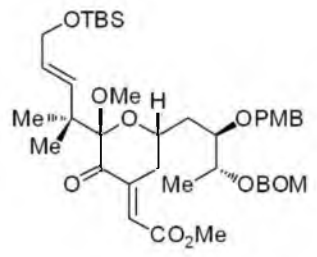
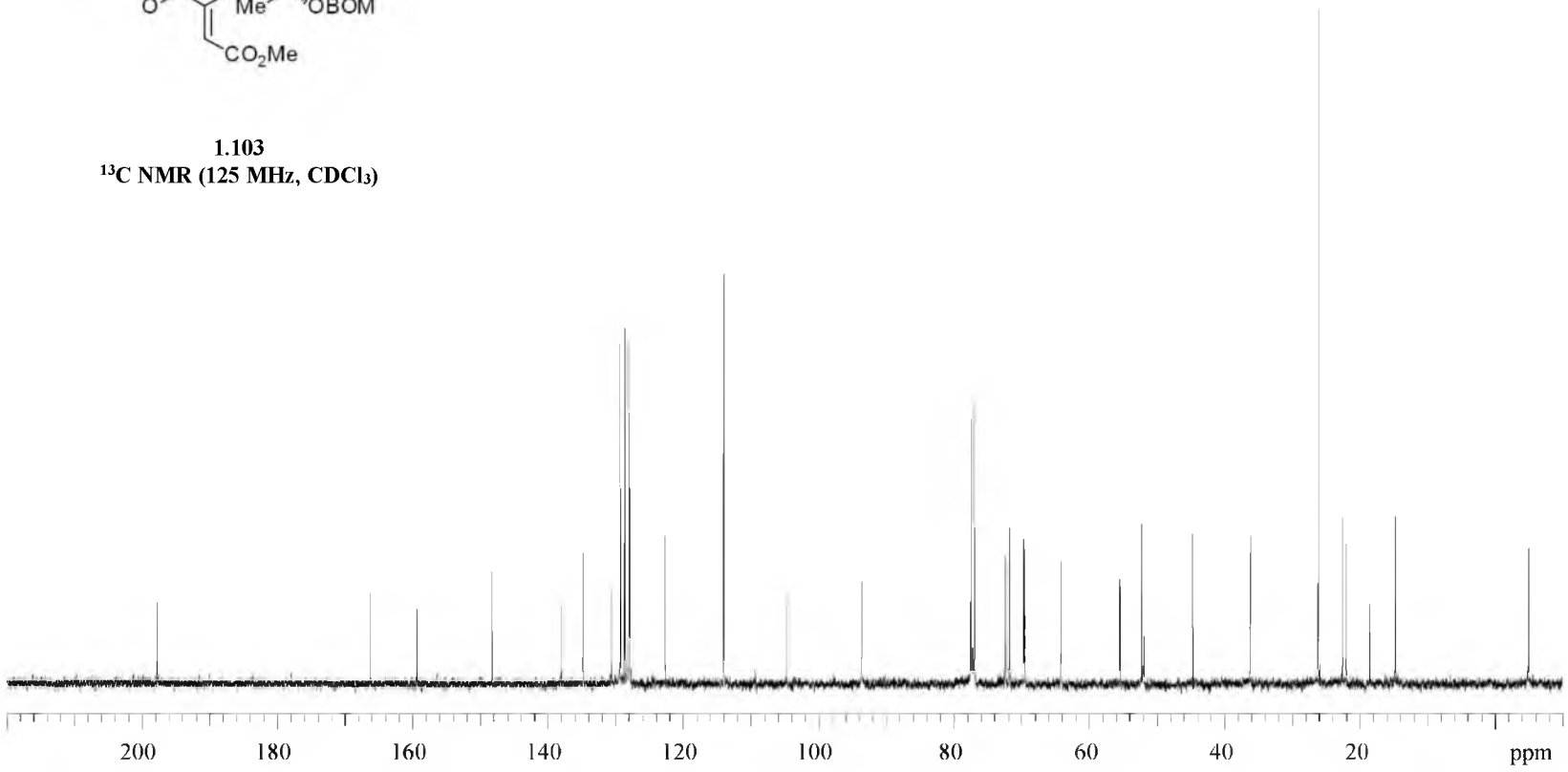
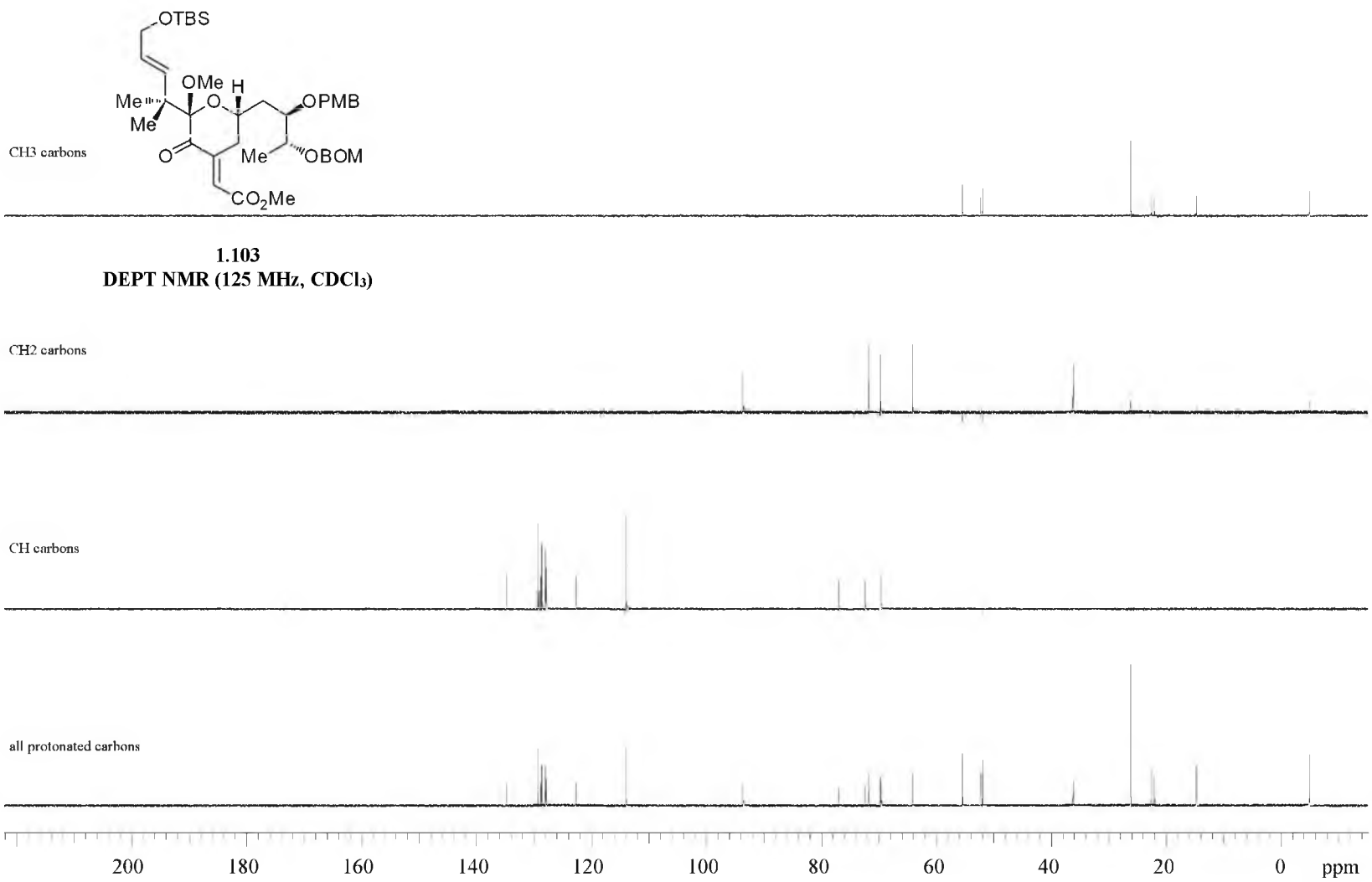
2
3
4

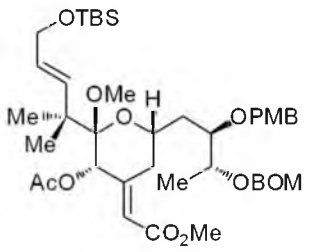


1.103
^{13}C NMR (125 MHz, $CDCl_3$)

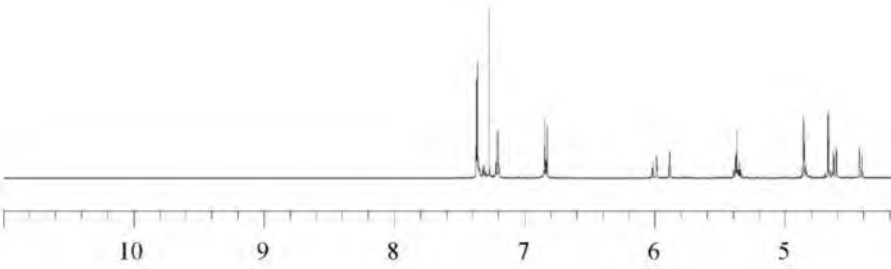




1.103
DEPT NMR (125 MHz, $CDCl_3$)



1.104
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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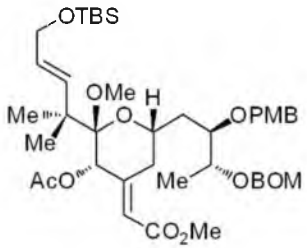
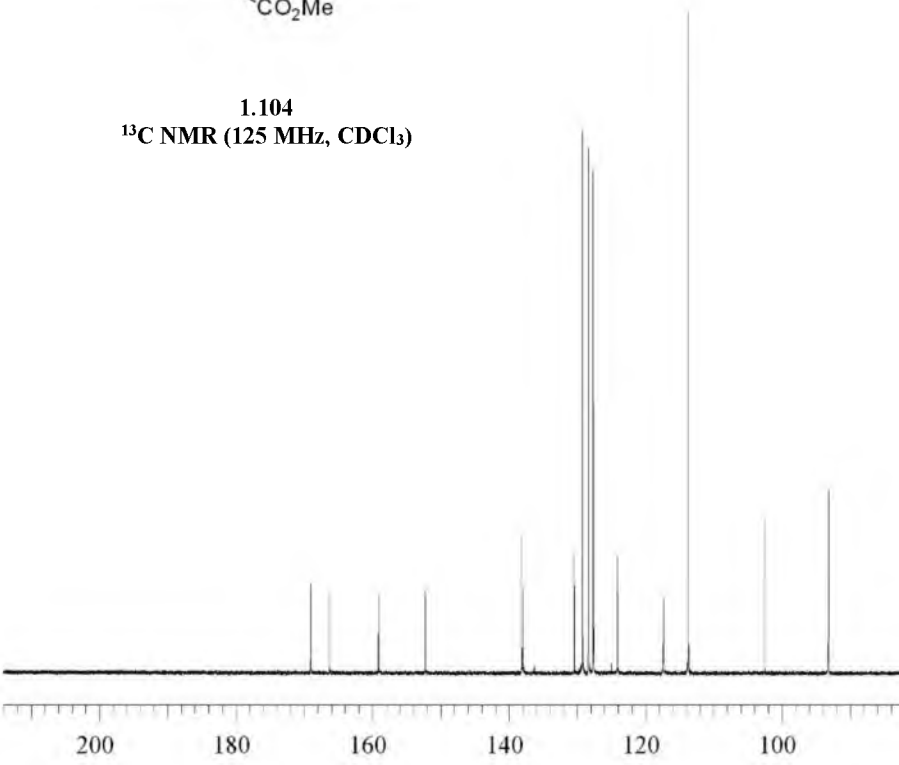
1
2
3
4



1.104
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
0
20
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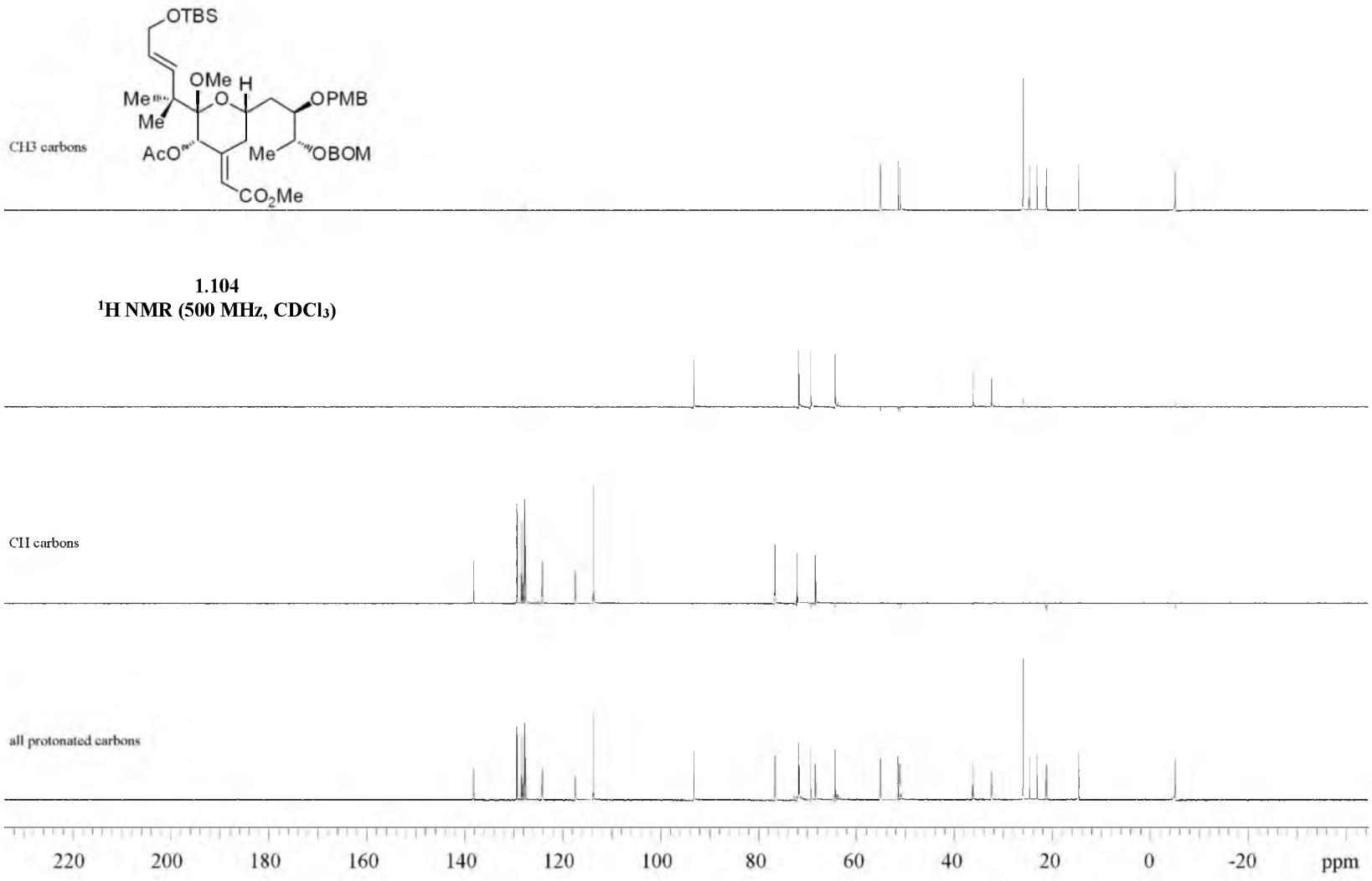
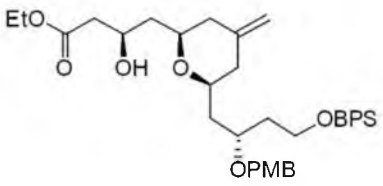
60
80



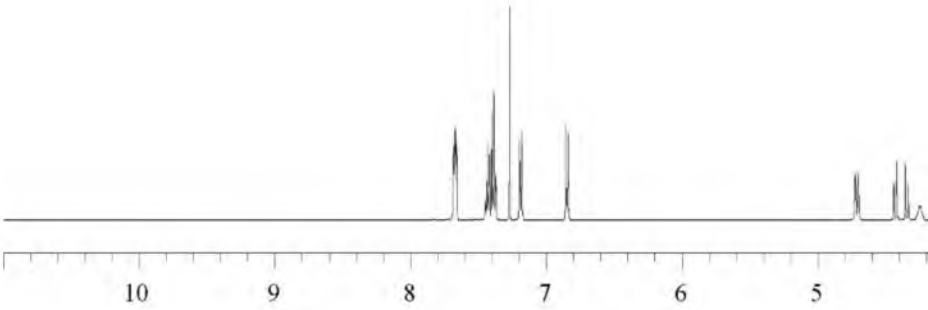
1.104
^{1}H NMR (500 MHz, $CDCl_3$)

APPENDIX B

^{1}H, ^{13}C, AND DEPT SPECTRA FOR CHAPTER 2



2.30
^{1}H NMR (500 MHz, $CDCl_3$)

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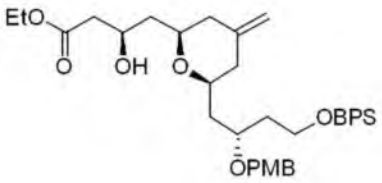
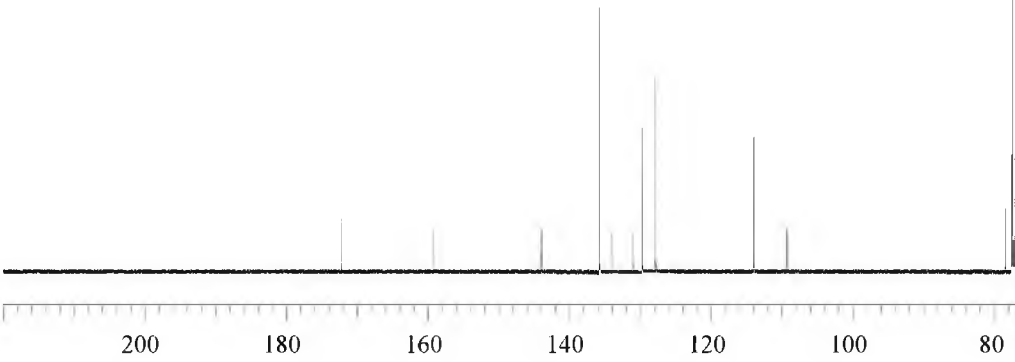


2.30
^{13}C NMR (125 MHz, $CDCl_3$)

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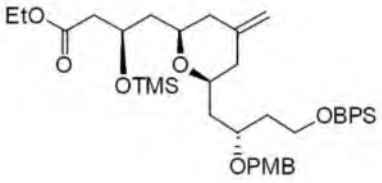
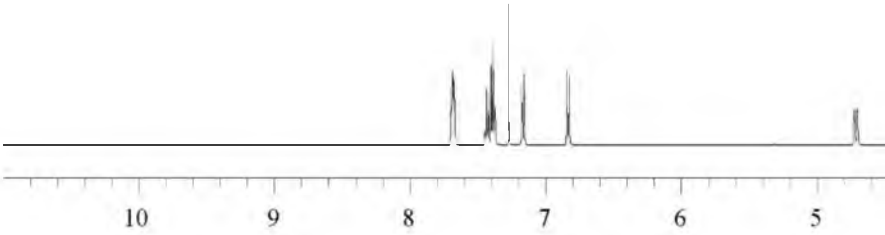
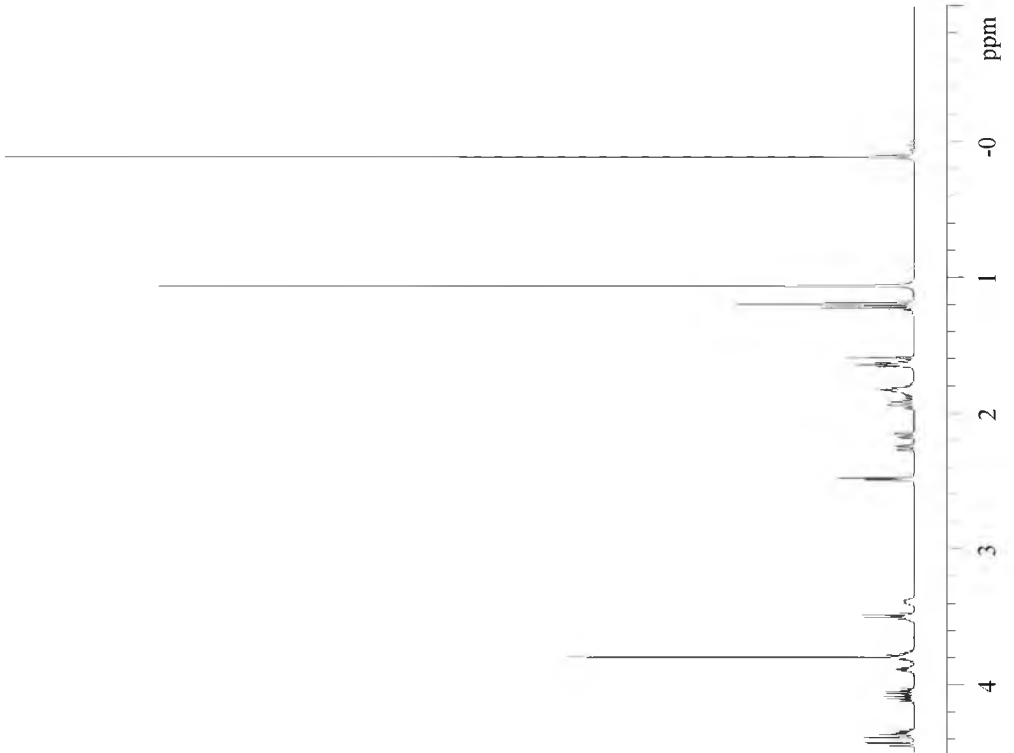


2.31
^{1}H NMR (500 MHz, $CDCl_3$)

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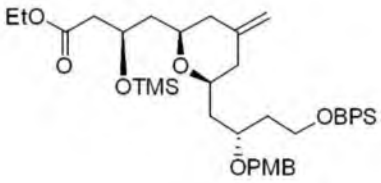
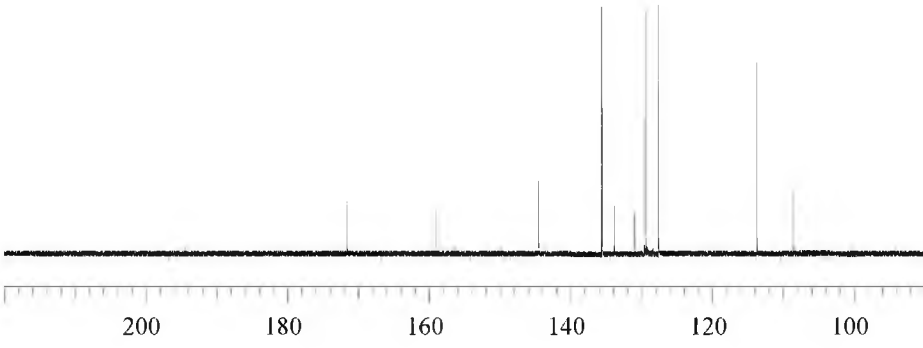
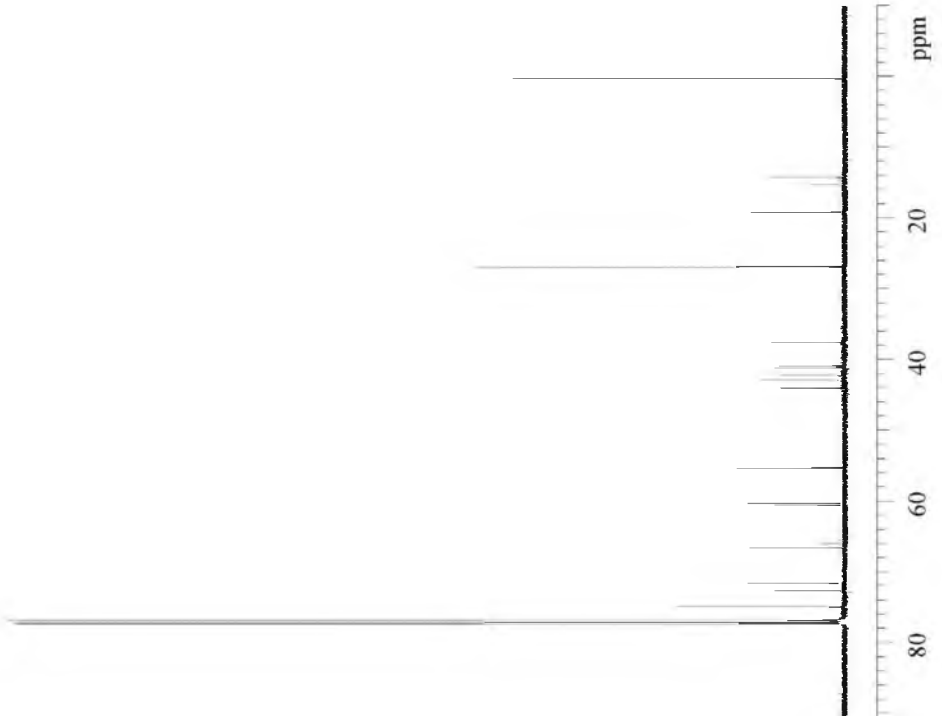


2.31
^{13}C NMR (125 MHz, $CDCl_3$)

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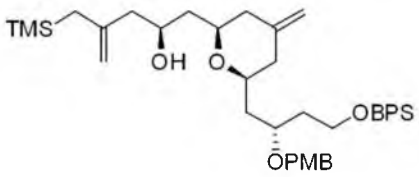
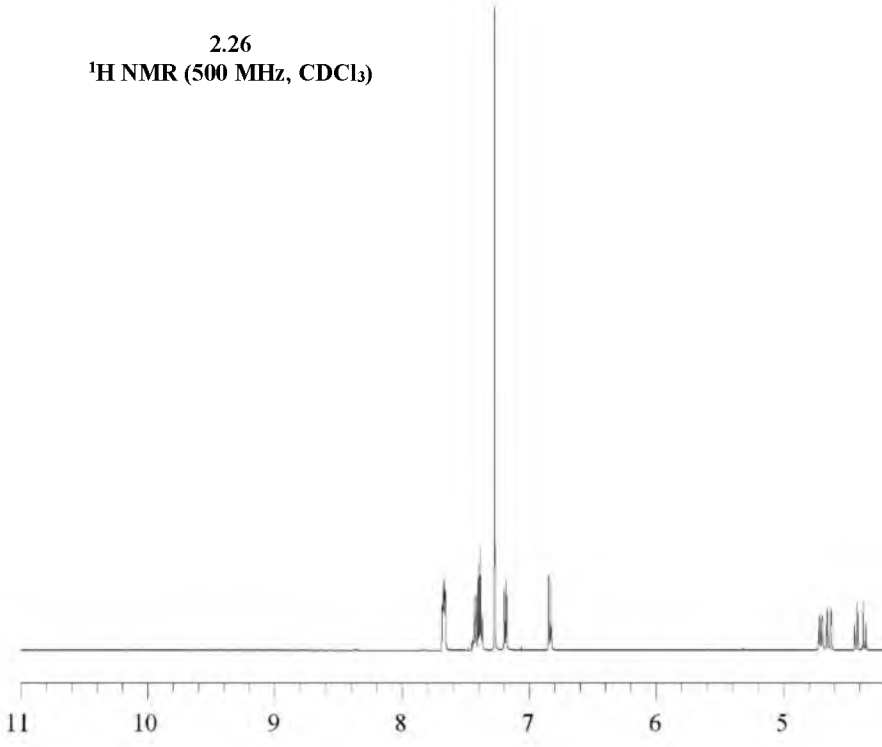


2.26
^{1}H NMR (500 MHz, $CDCl_3$)

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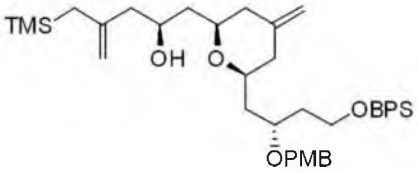
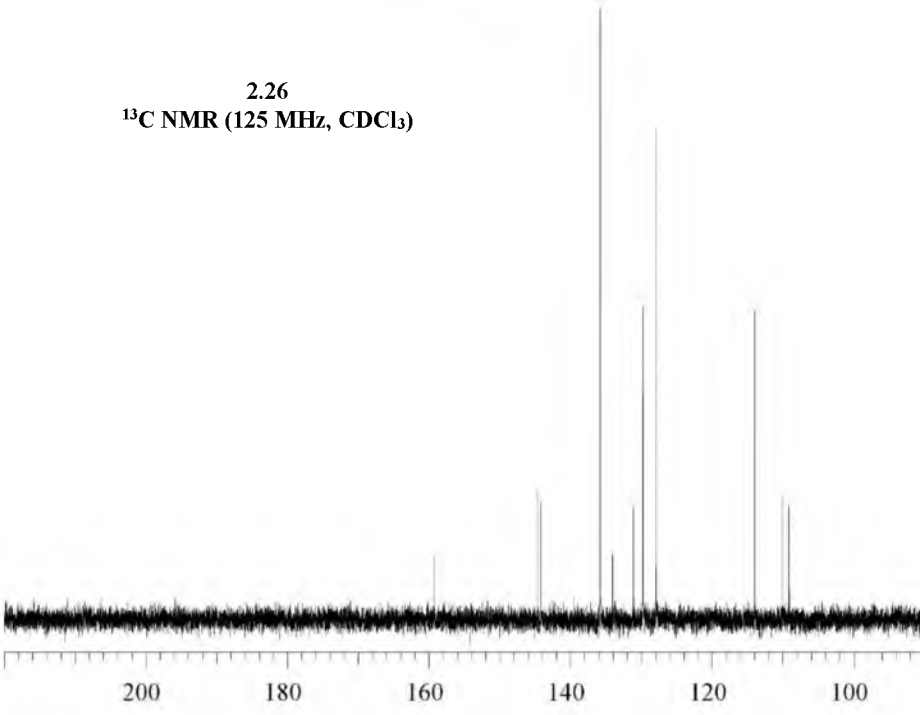


2.26
^{13}C NMR (125 MHz, $CDCl_3$)

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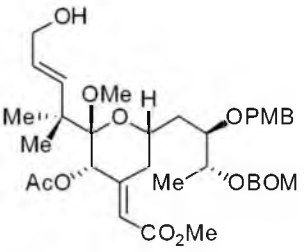
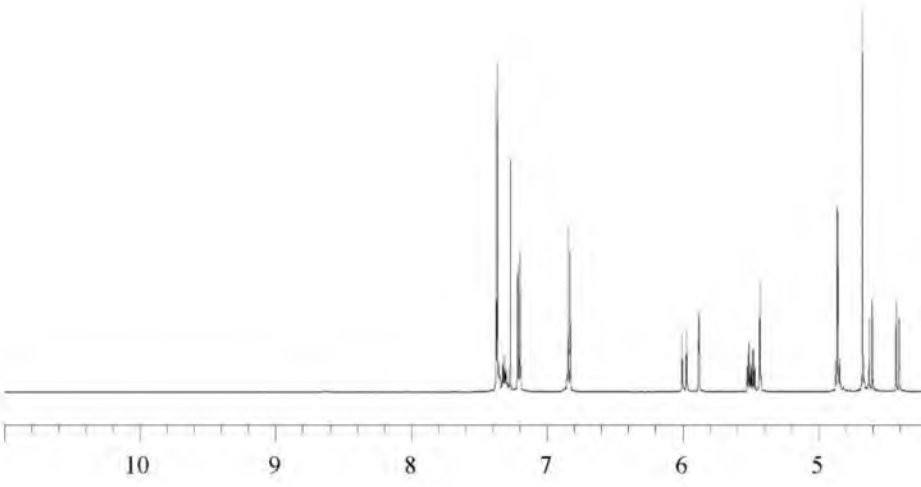
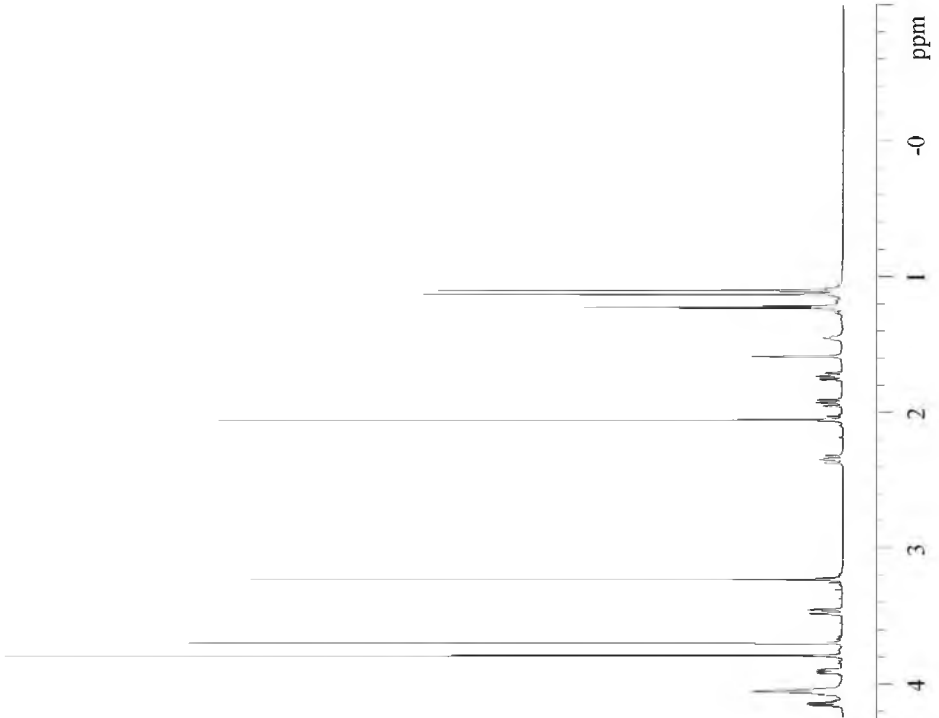


2.33
^{1}H NMR (500 MHz, $CDCl_3$)

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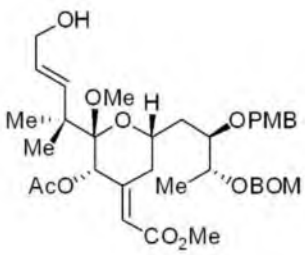
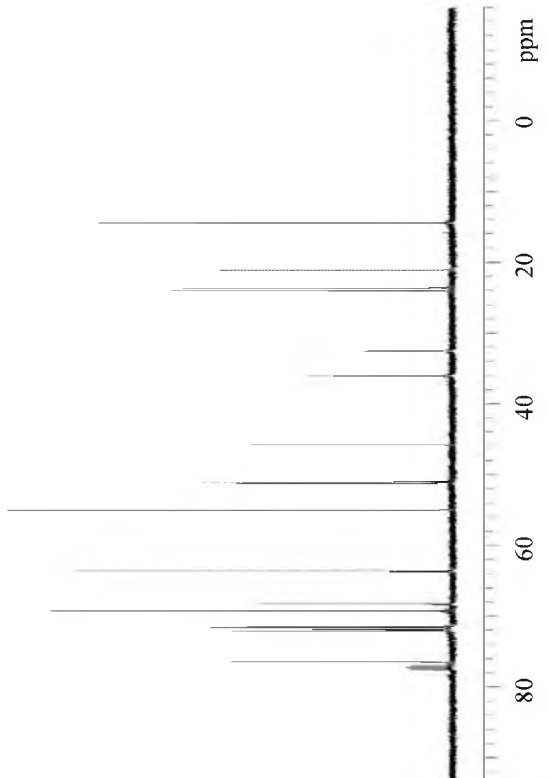


2.33
^{13}C NMR (125 MHz, $CDCl_3$)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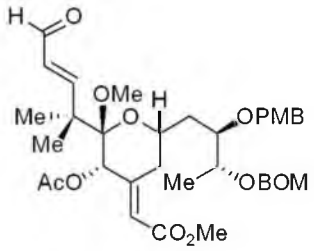
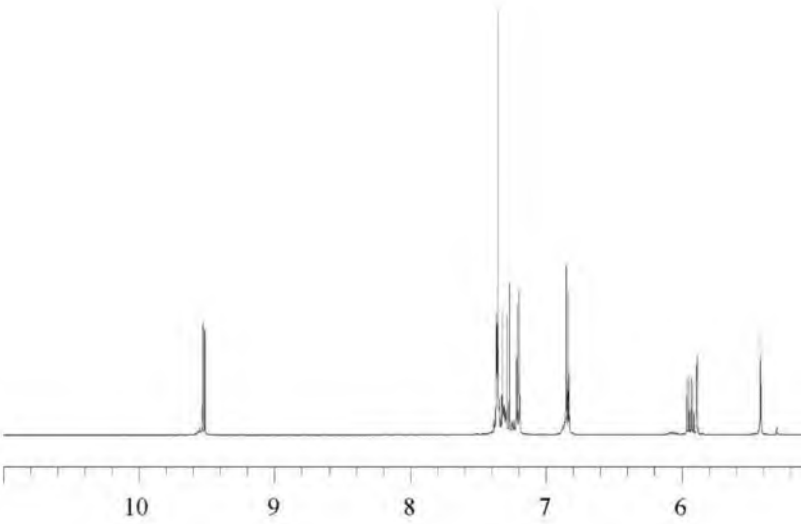


2.34
^{1}H NMR (500 MHz, $CDCl_3$)



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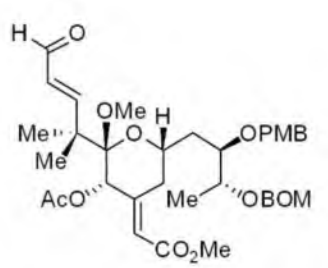
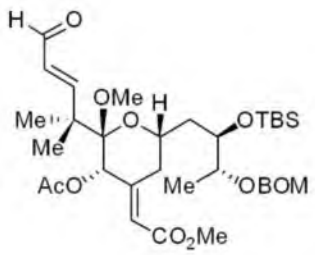
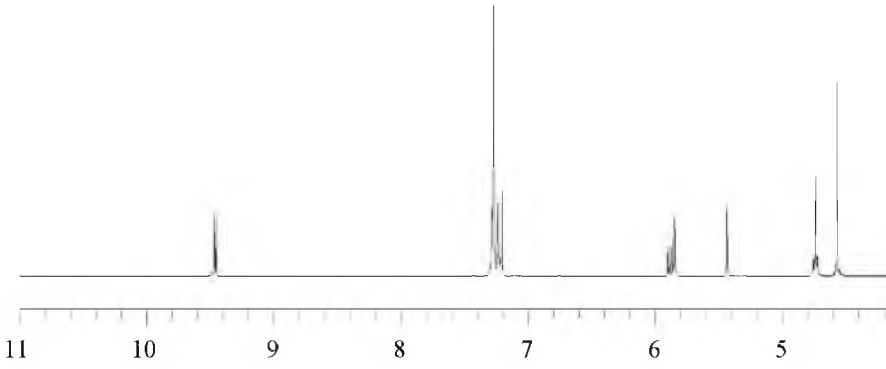
ppm



2.34
^{13}C NMR (125 MHz, $CDCl_3$)



2.25
^{1}H NMR (500 MHz, $CDCl_3$)

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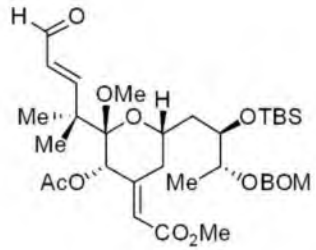
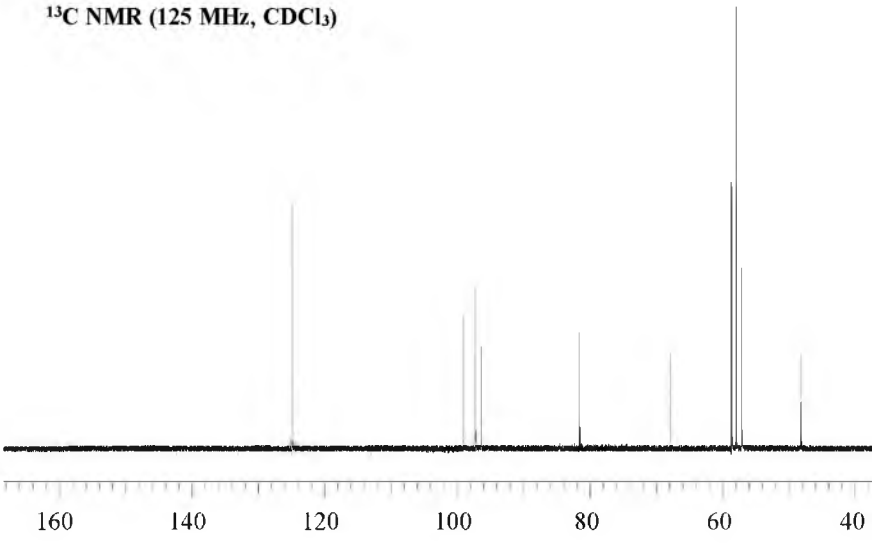


2.25

^{13}C NMR (125 MHz, $CDCl_3$)

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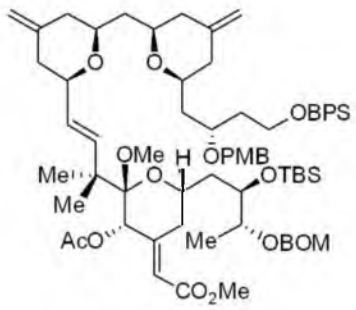

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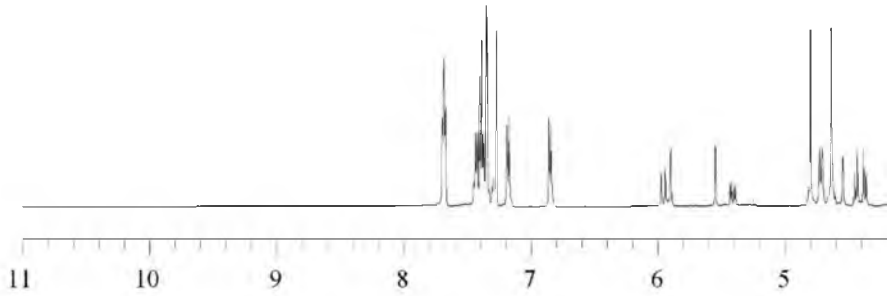
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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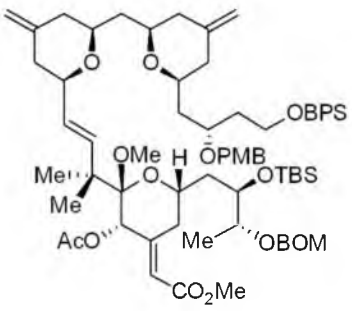
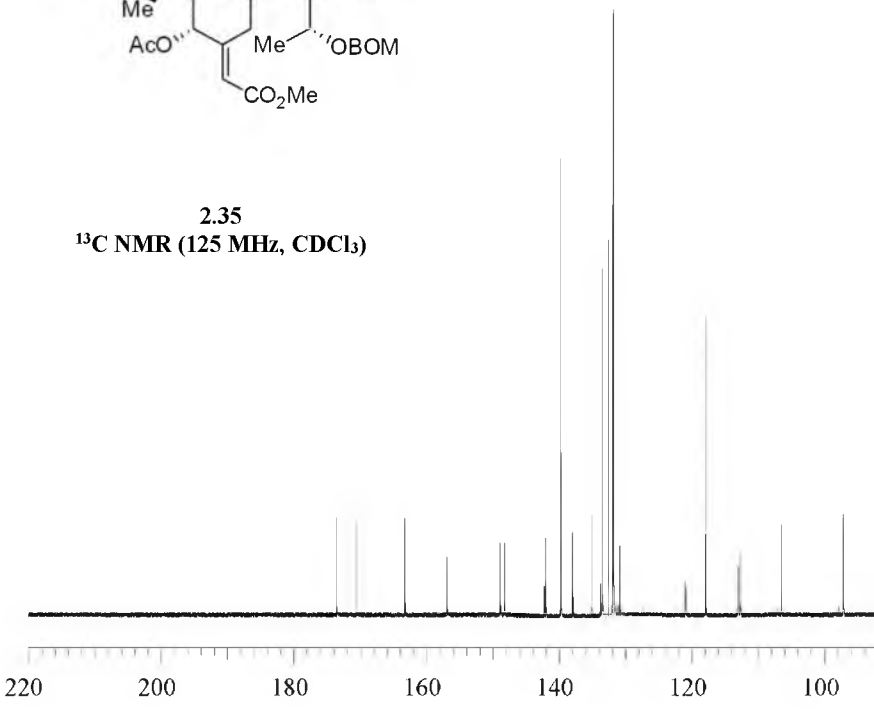
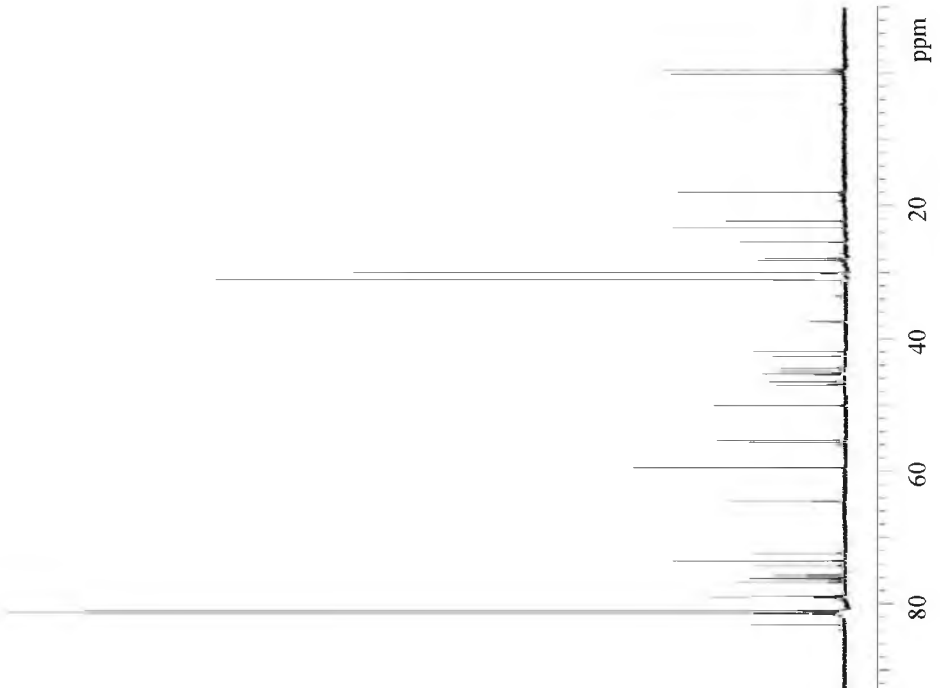


2.35
^{13}C NMR (125 MHz, $CDCl_3$)

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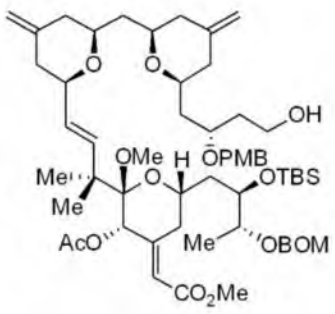
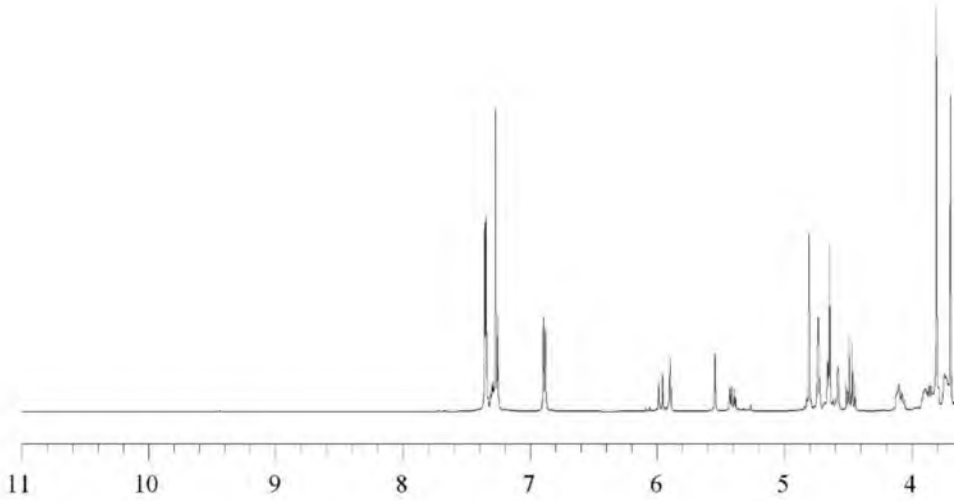


2.36

^{1}H NMR (500 MHz, $CDCl_3$)

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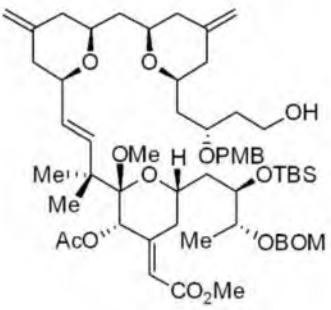
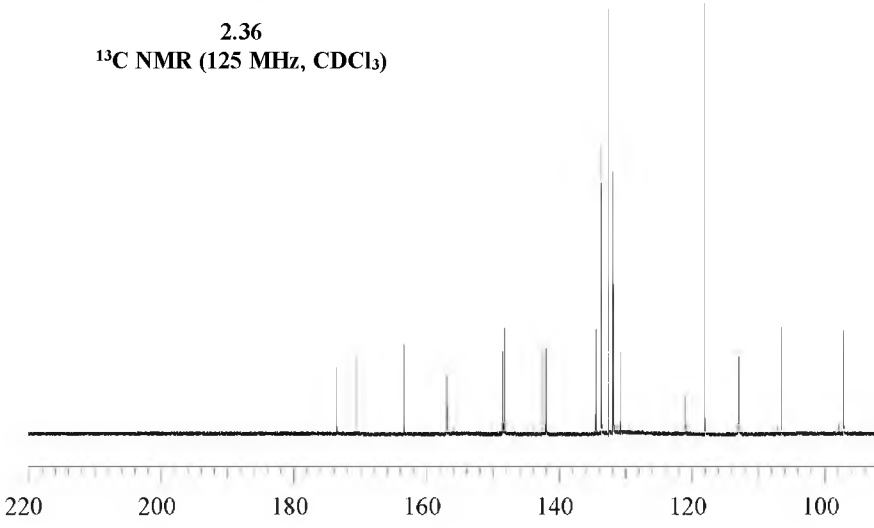


2.36
^{13}C NMR (125 MHz, $CDCl_3$)

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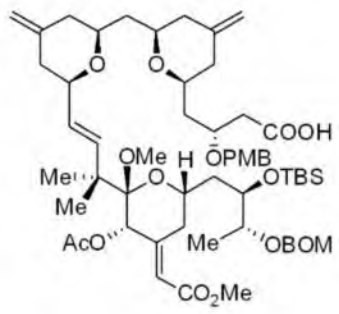

2.37
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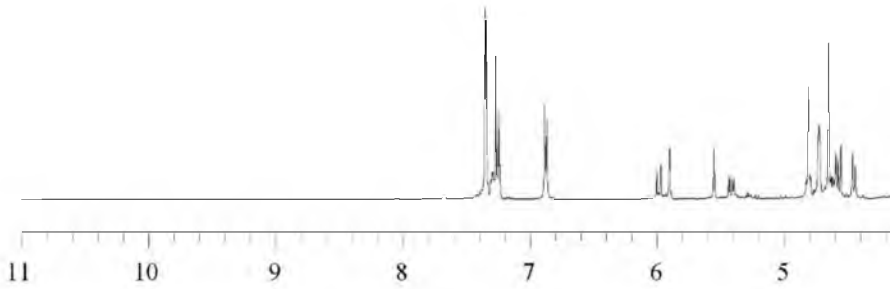


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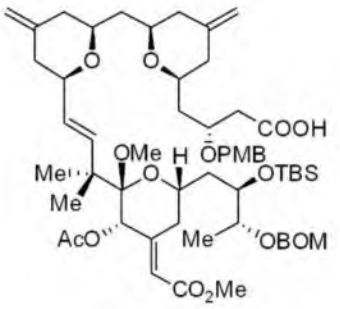
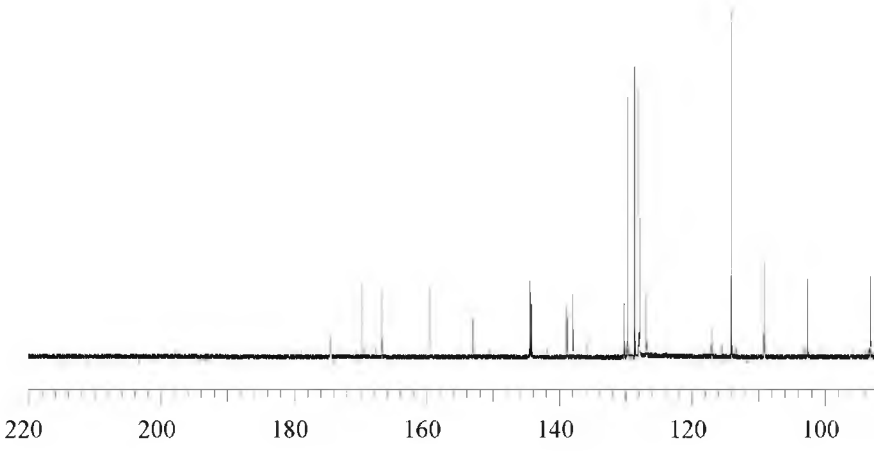
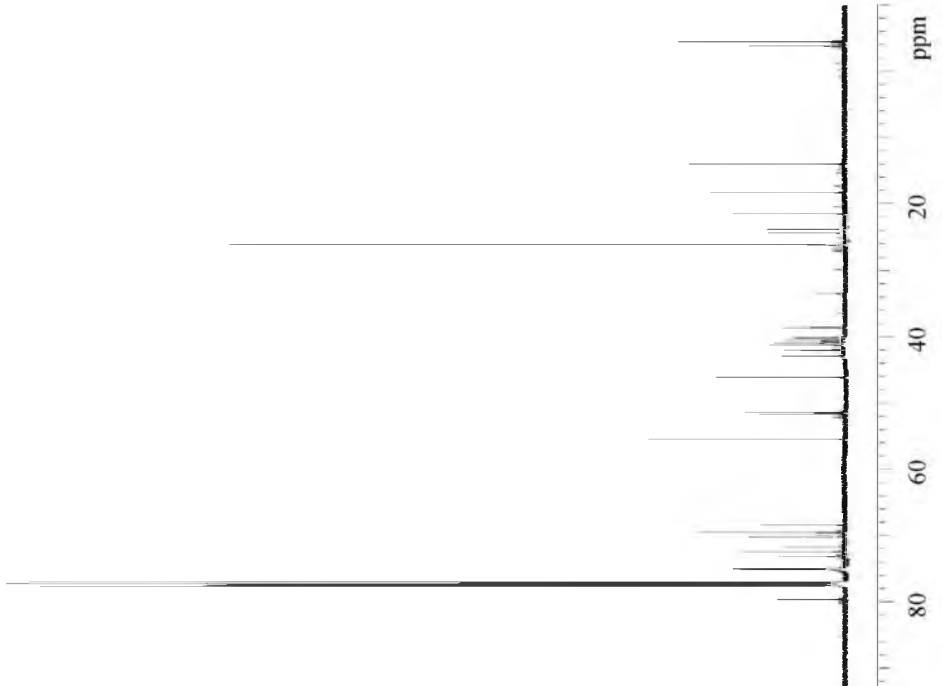


2.37

^{13}C NMR (125 MHz, $CDCl_3$)

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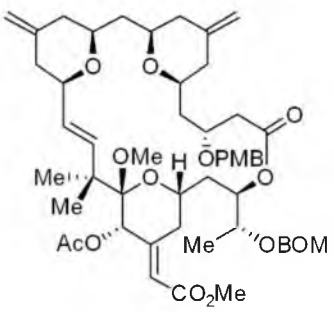
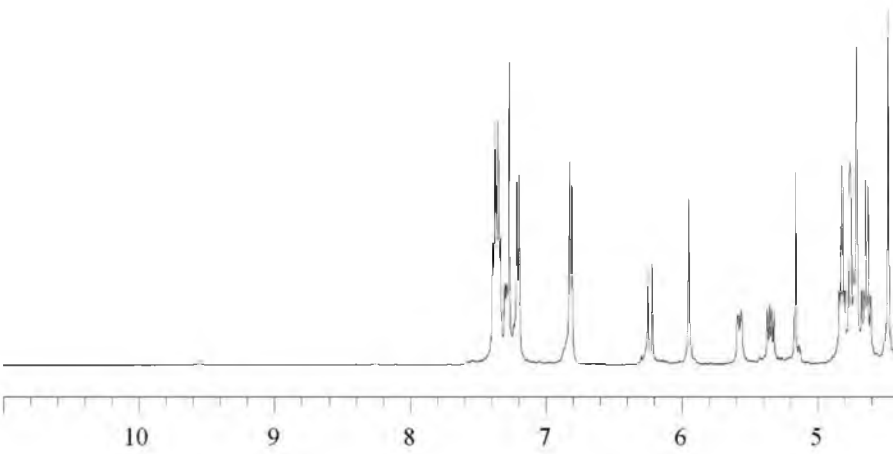
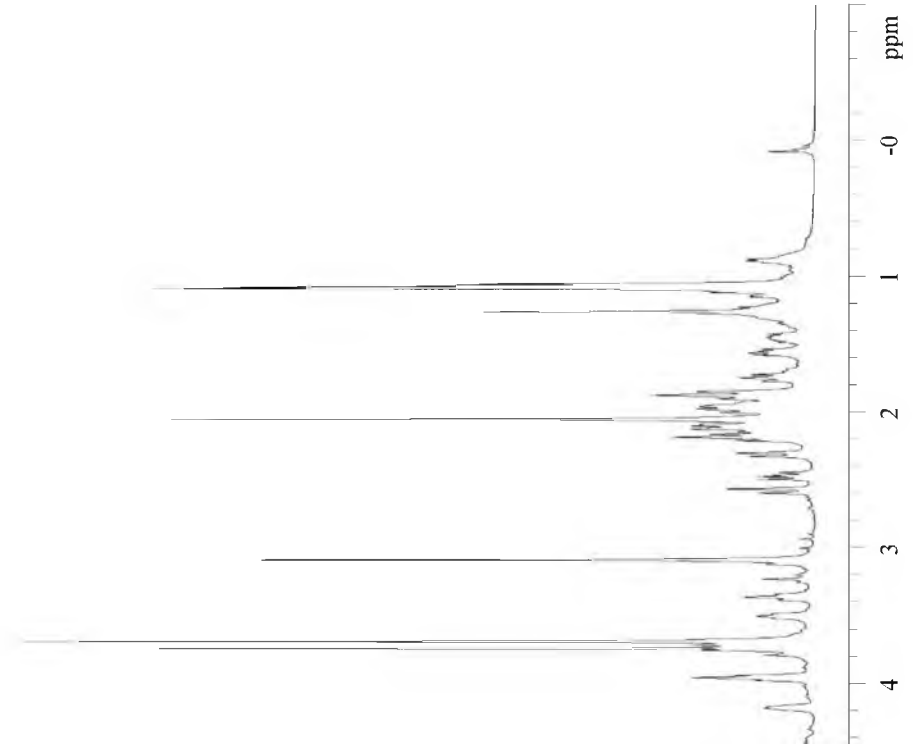


2.24
^{1}H NMR (500 MHz, $CDCl_3$)

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3
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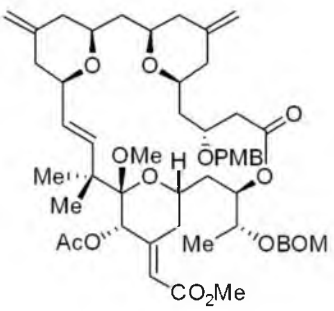
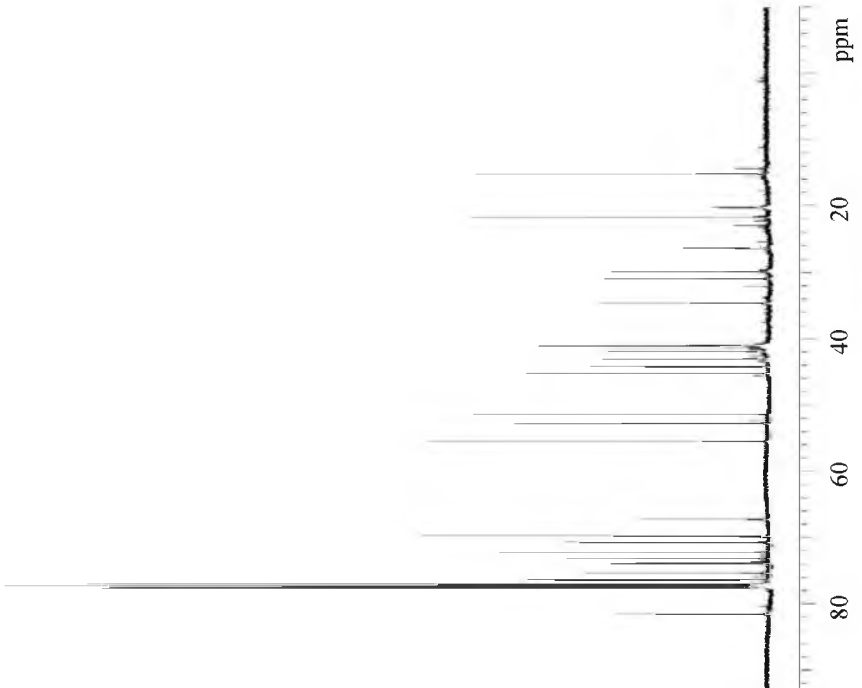


2.24
^{13}C NMR (125 MHz, $CDCl_3$)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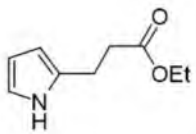
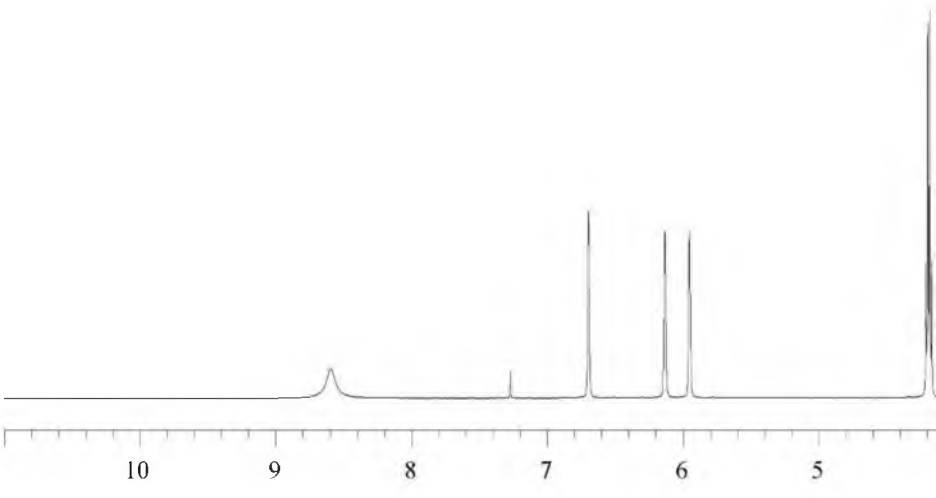


2.39
^{1}H NMR (500 MHz, $CDCl_3$)

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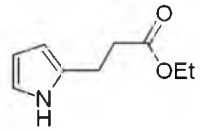
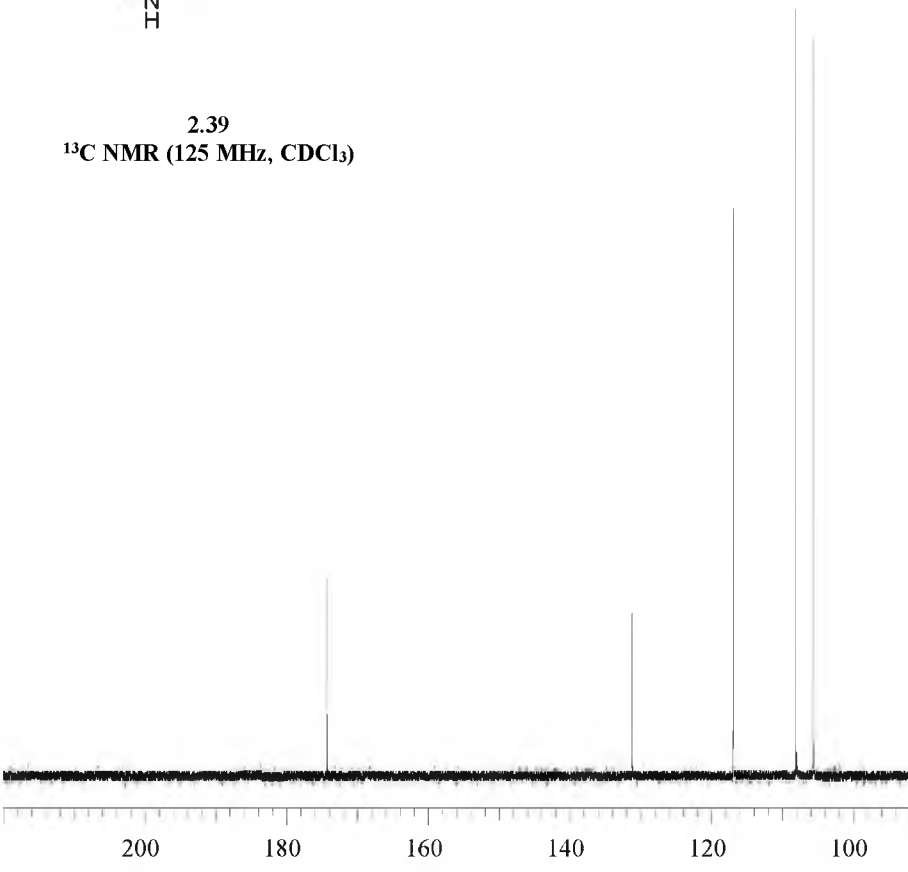


2.39
^{13}C NMR (125 MHz, $CDCl_3$)

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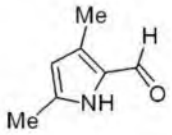
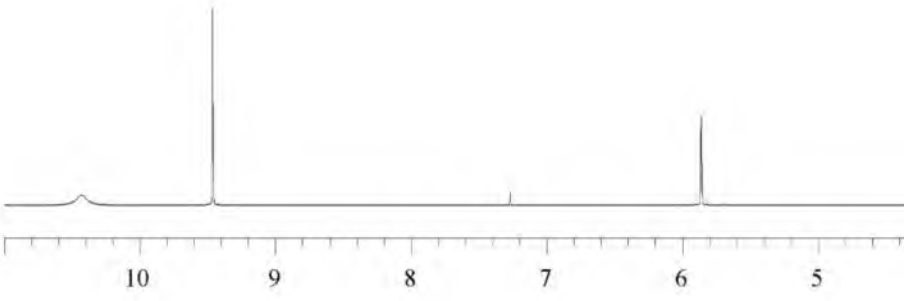
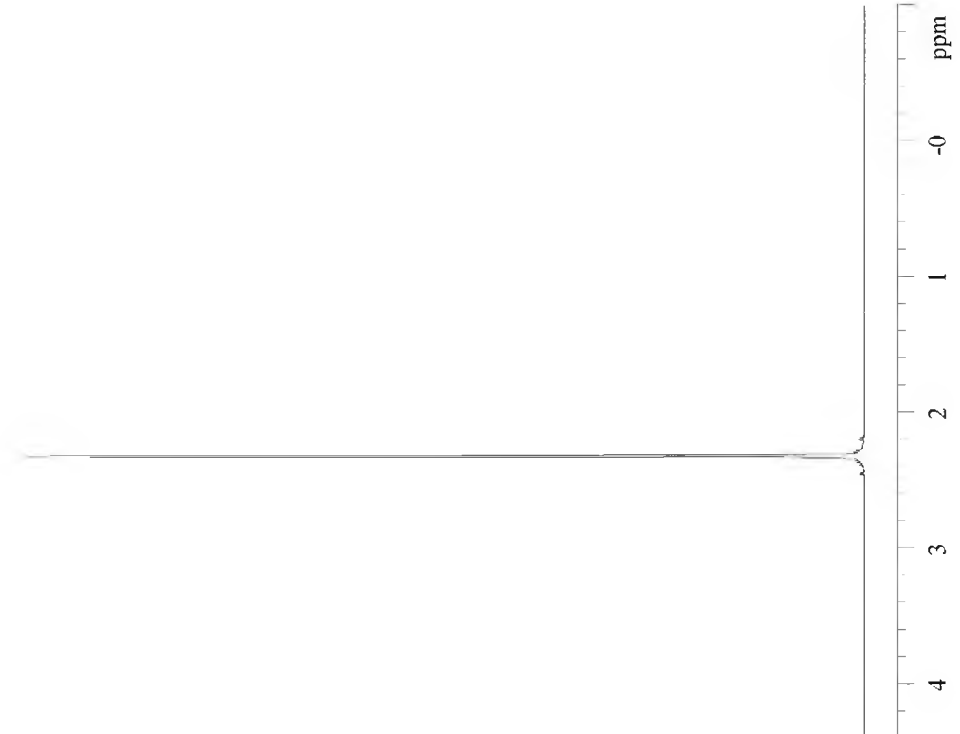


2.40
^{1}H NMR (500 MHz, $CDCl_3$)

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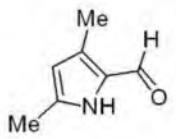
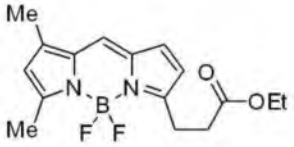
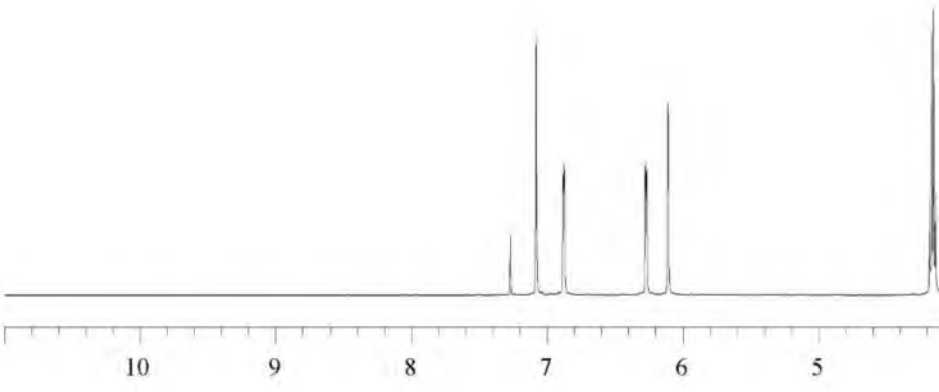


2.40
^{13}C NMR (125 MHz, $CDCl_3$)



2.41
^{1}H NMR (500 MHz, $CDCl_3$)

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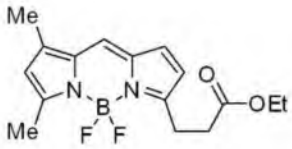
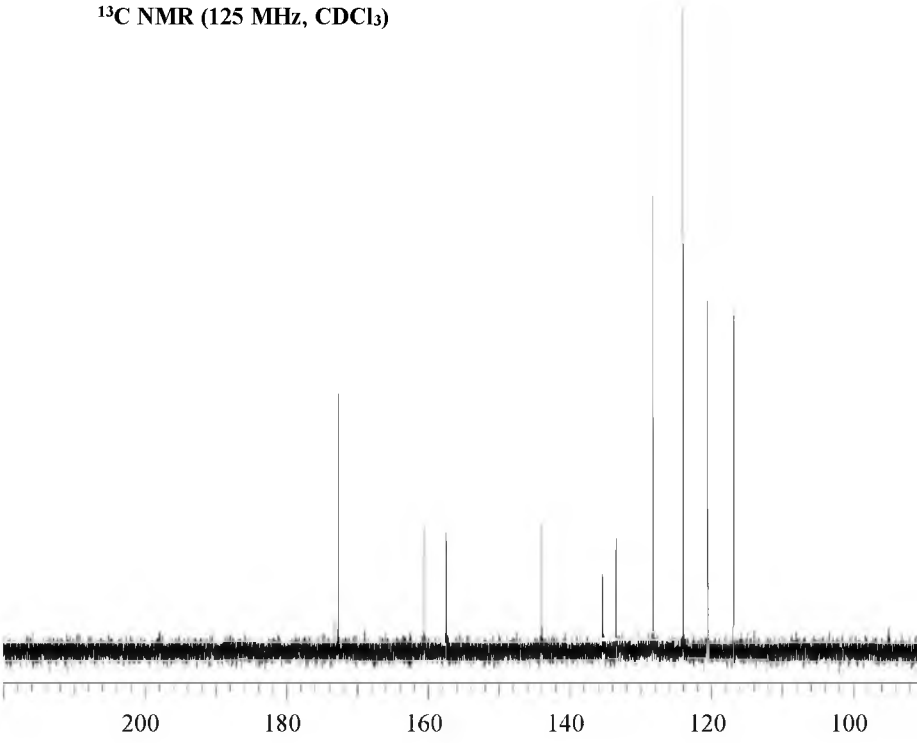
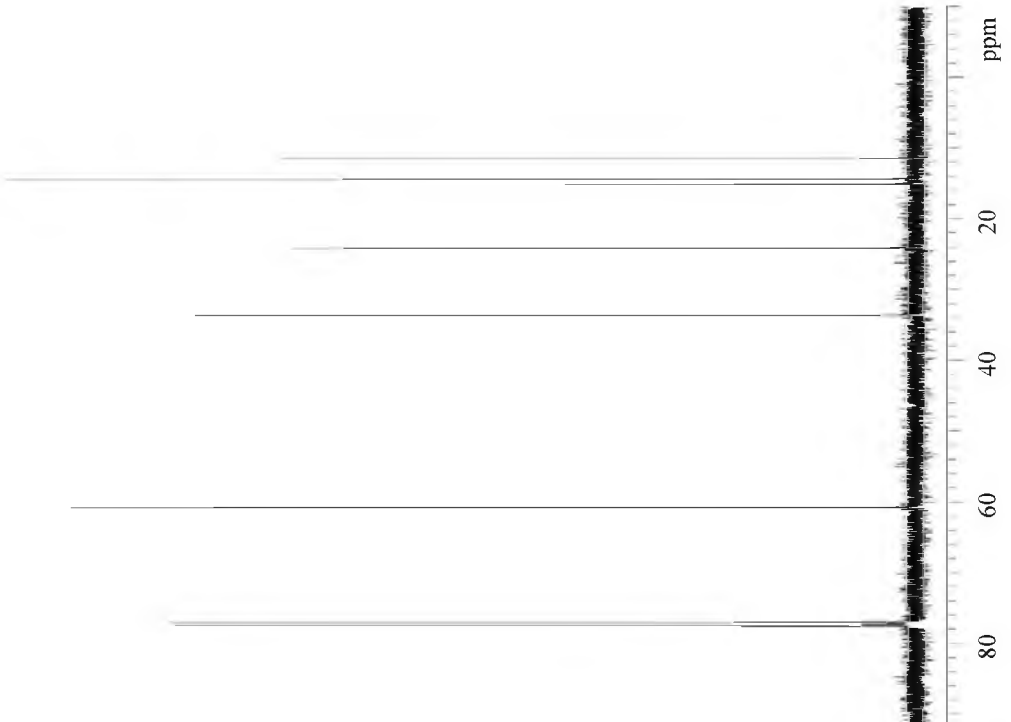


2.41
^{13}C NMR (125 MHz, $CDCl_3$)

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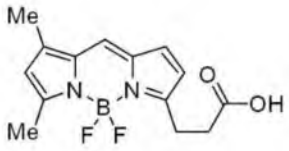
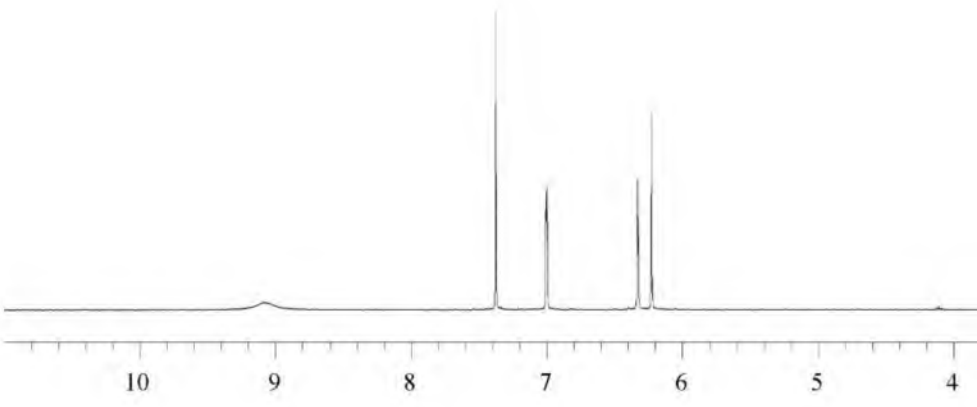


2.42
^{1}H NMR (500 MHz, CD_3CN)




ppm
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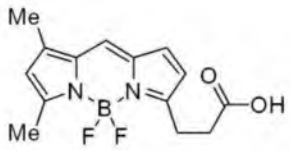
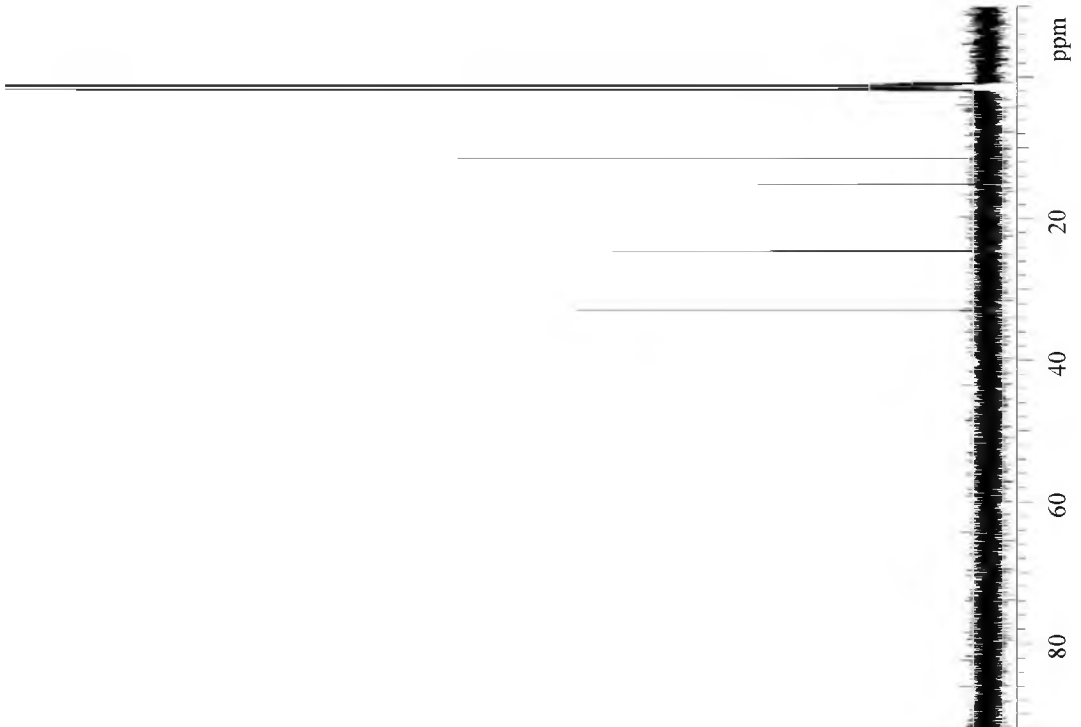


2.42
^{13}C NMR (125 MHz, CD_3CN)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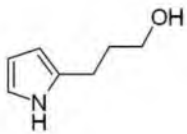
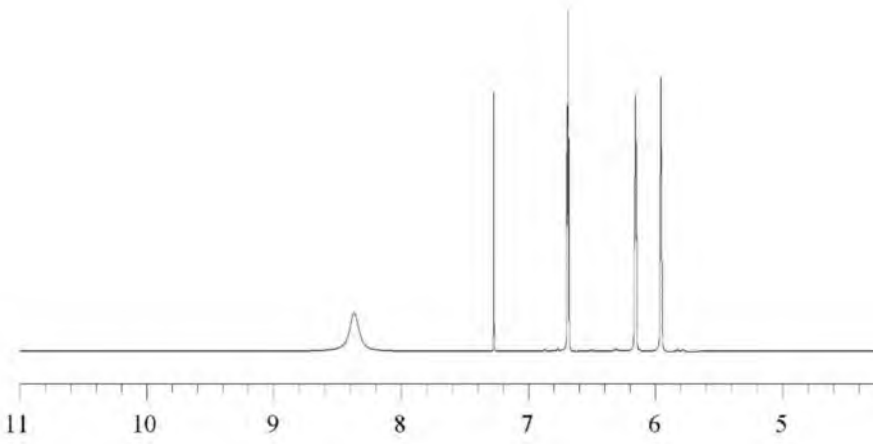
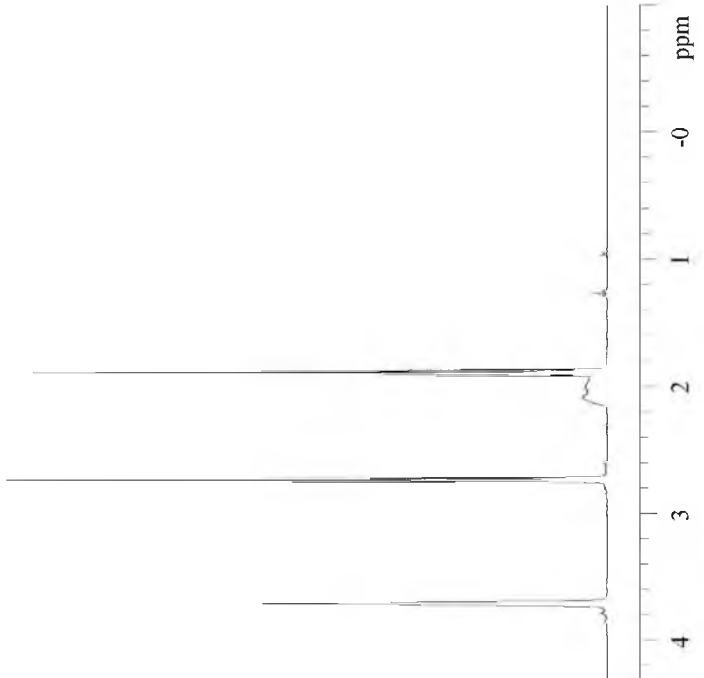


2.48
^{1}H NMR (500 MHz, CD_3CN)

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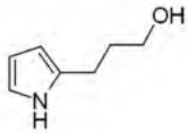
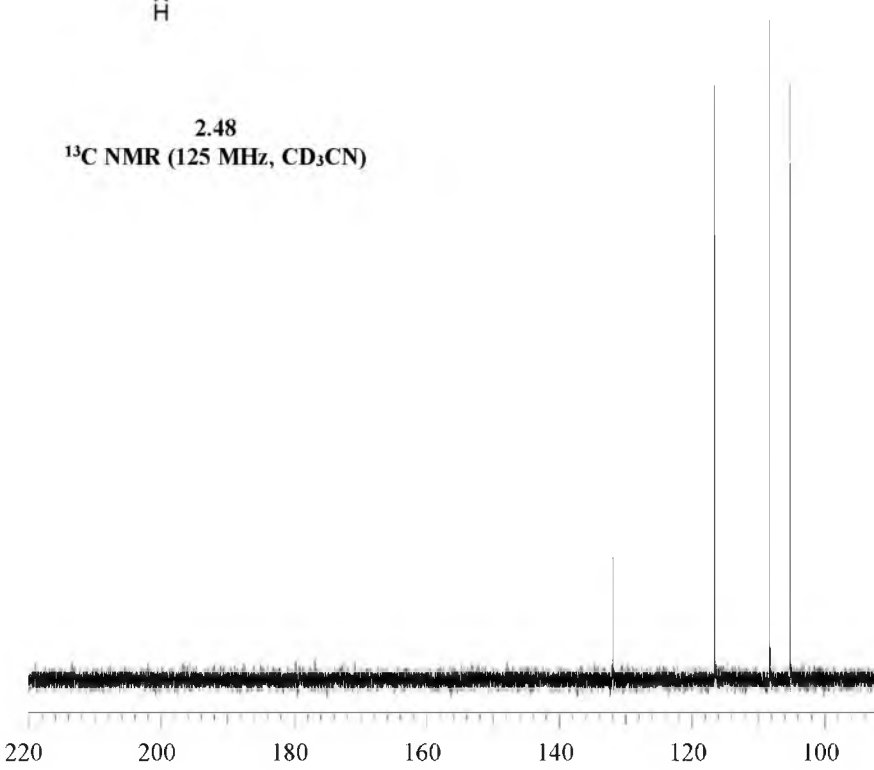


2.48
^{13}C NMR (125 MHz, CD_3CN)

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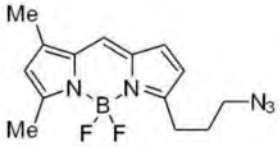
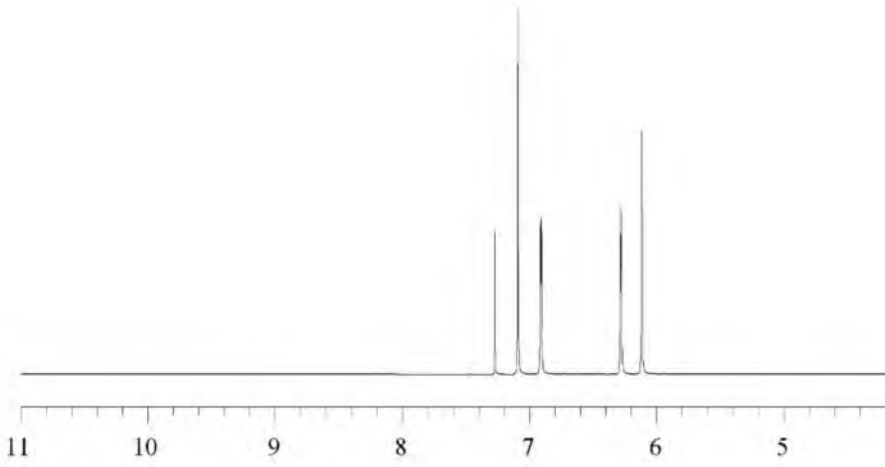


2.47
^{1}H NMR (500 MHz, CD_3CN)




ppm
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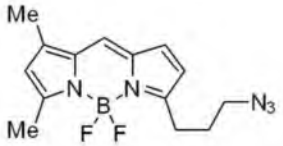
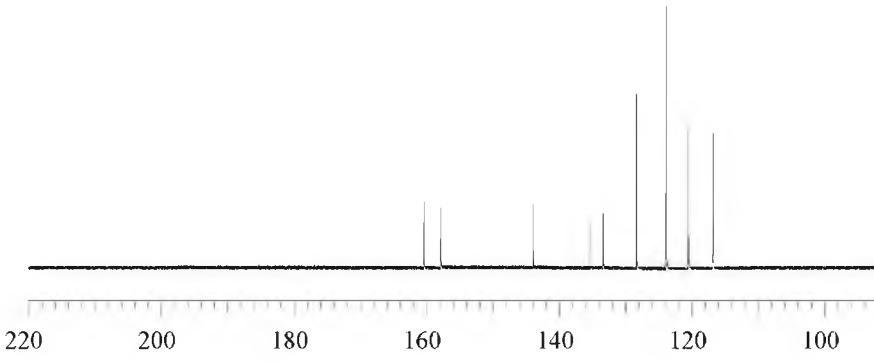


2.47
^{13}C NMR (125 MHz, CD_3CN)

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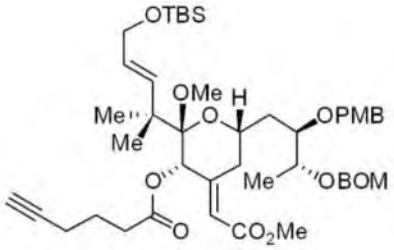
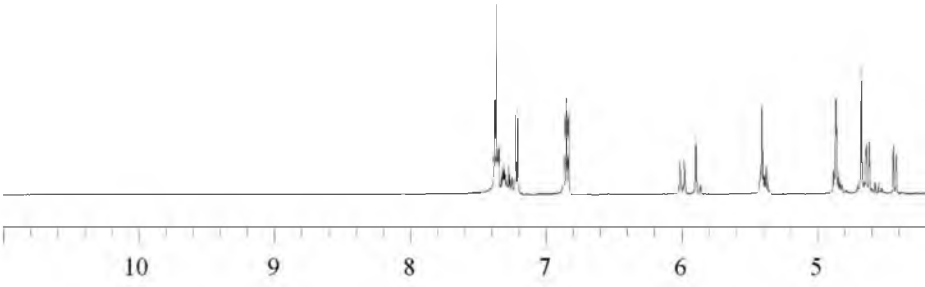


2.50
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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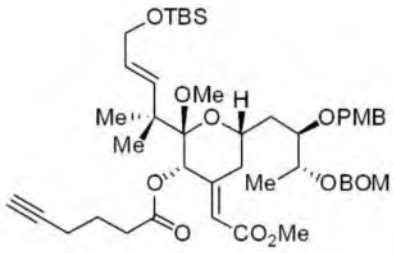
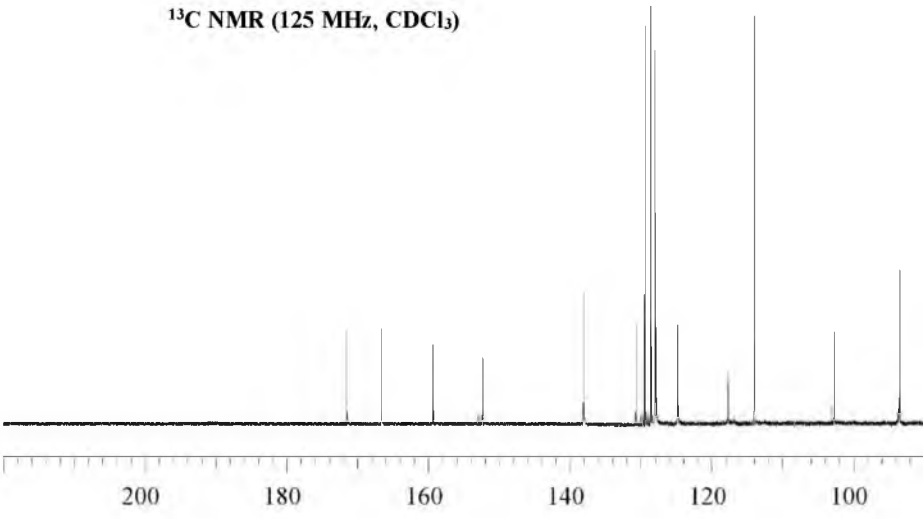


2.50

^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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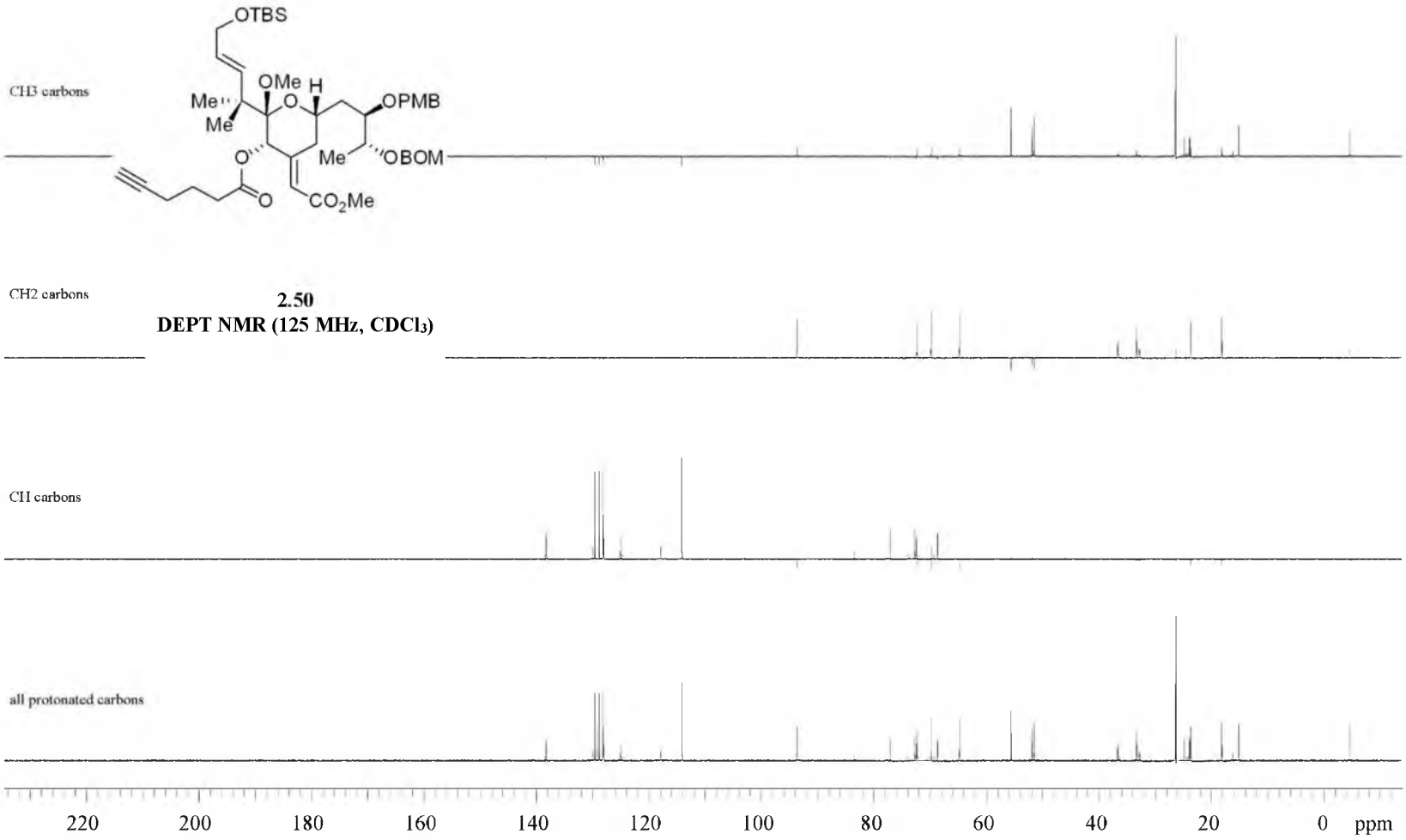
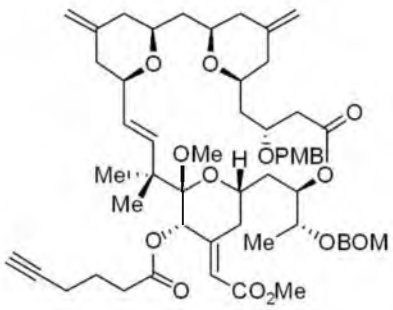
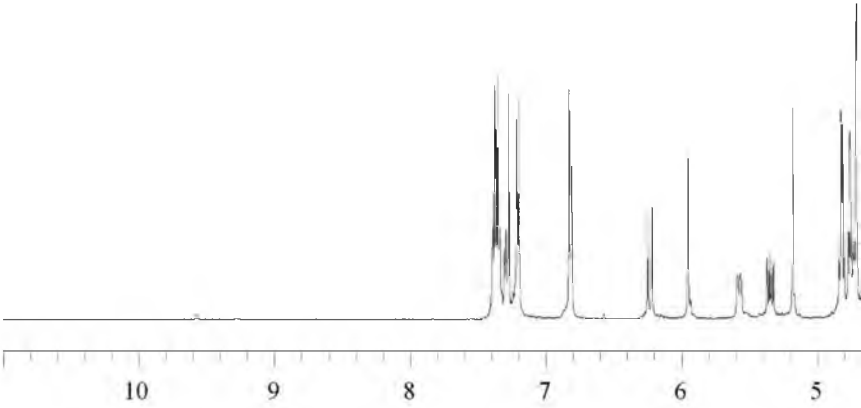


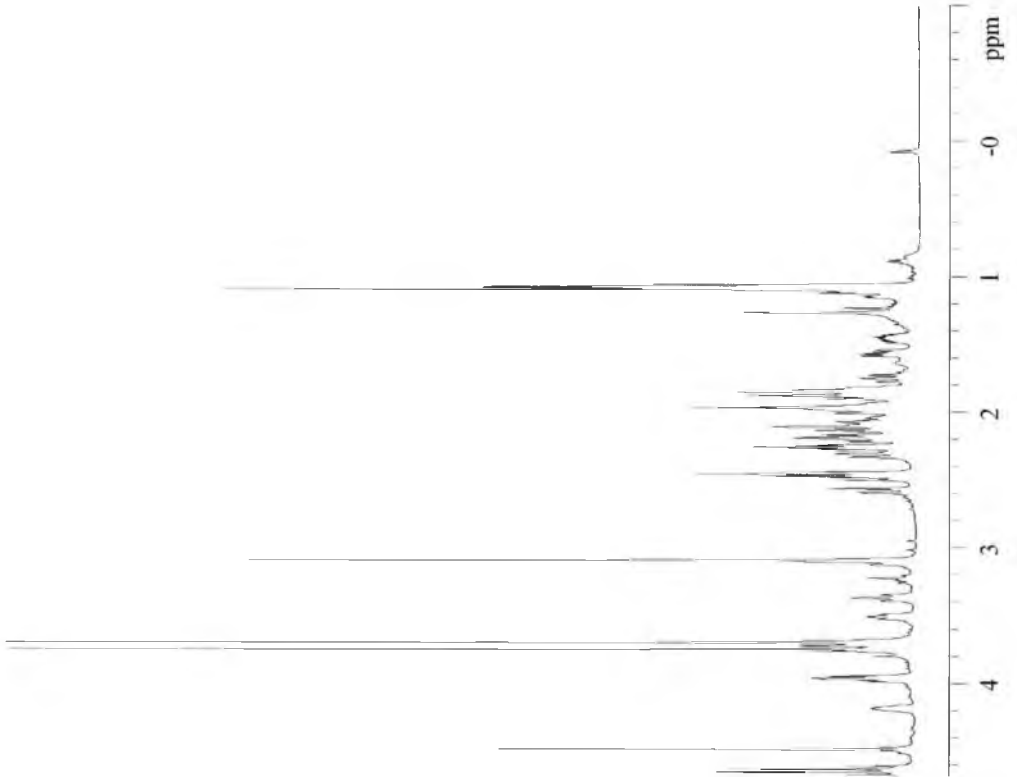
2.50

DEPT NMR (125 MHz, $CDCl_3$)



2.52
^{1}H NMR (500 MHz, $CDCl_3$)

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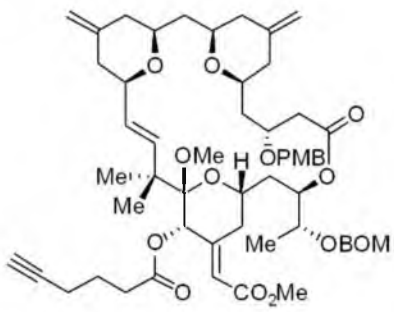
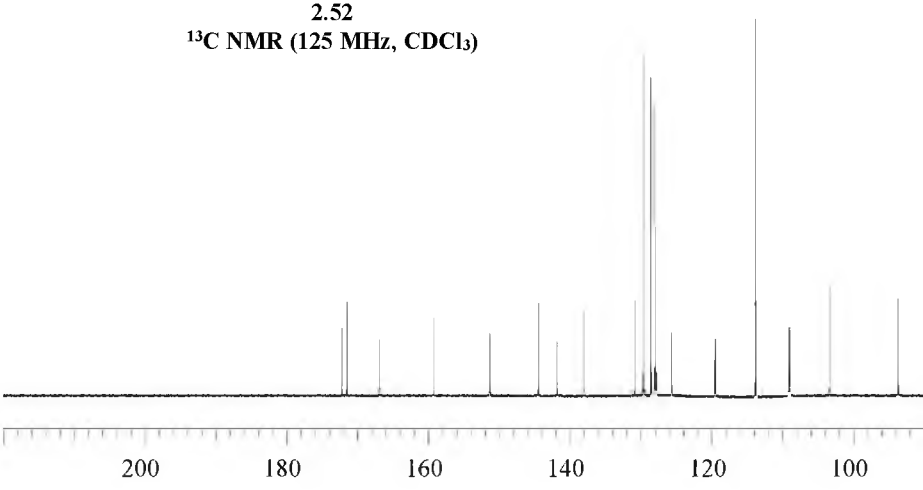
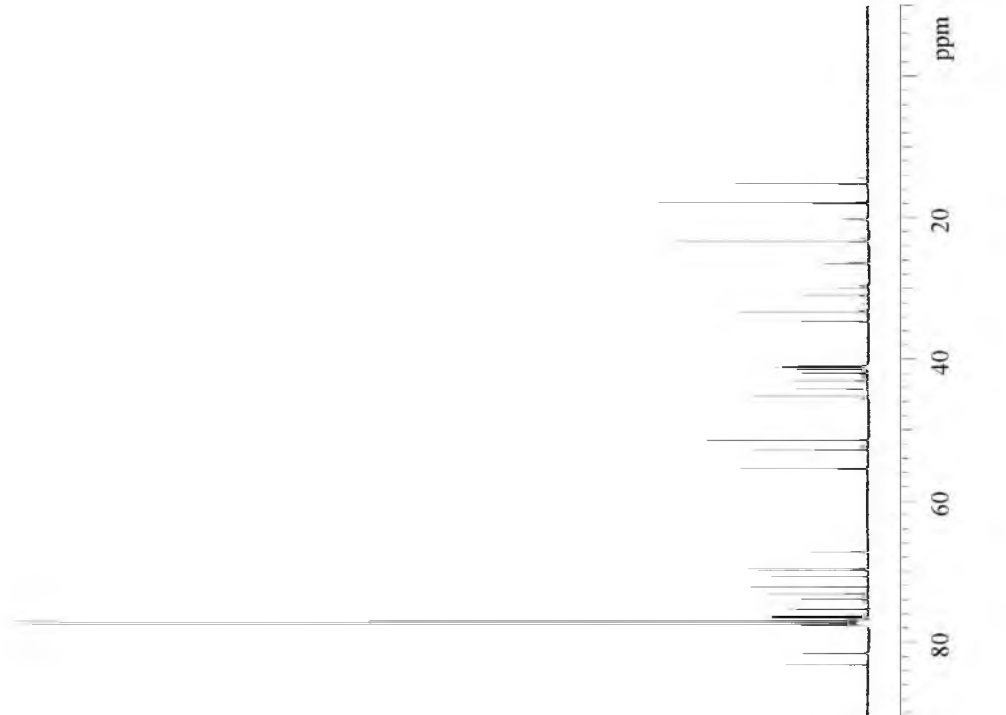
ppm



2.52
^{13}C NMR (125 MHz, $CDCl_3$)

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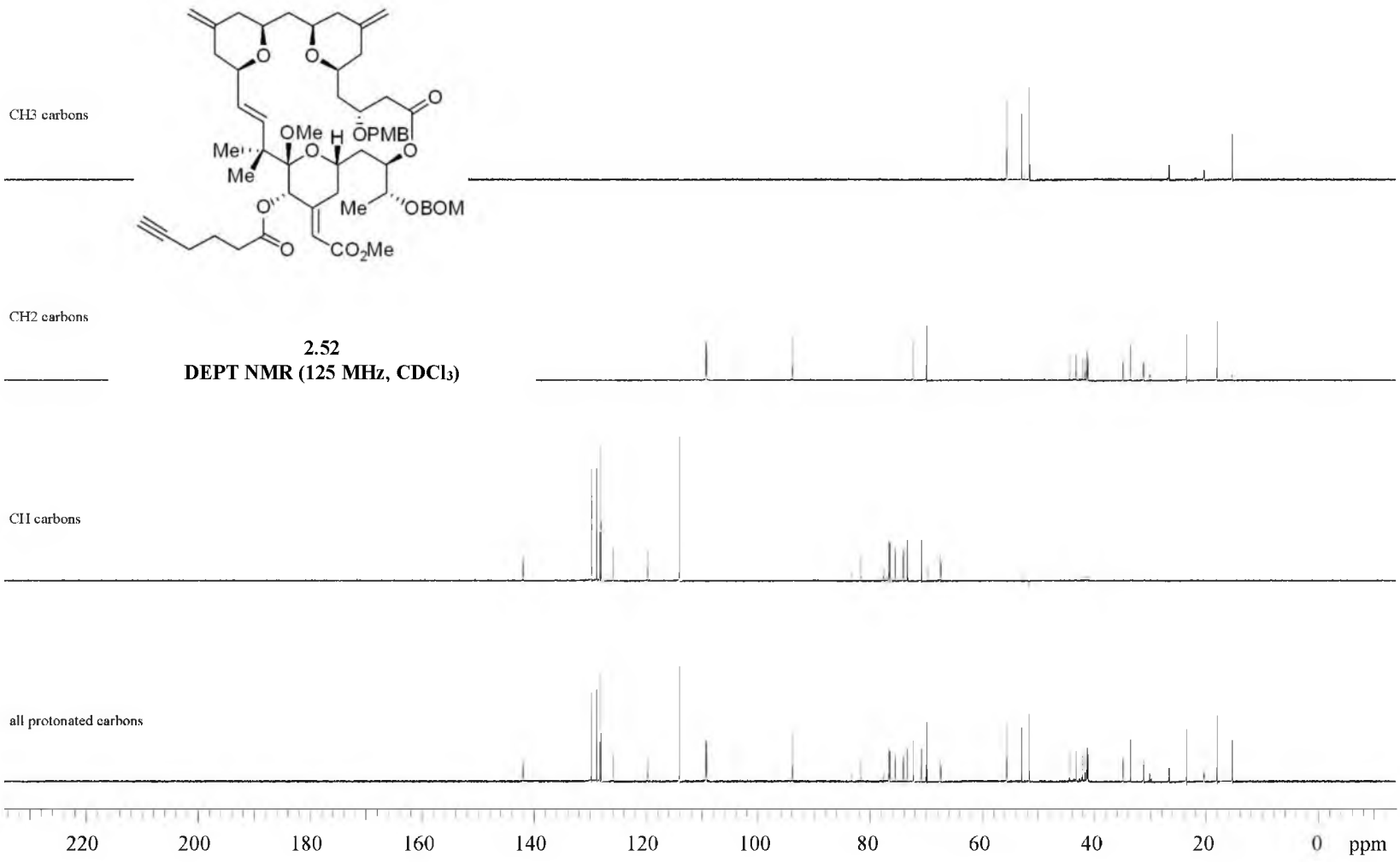
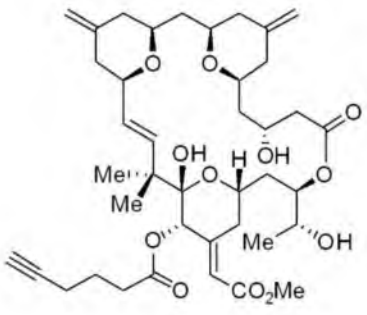
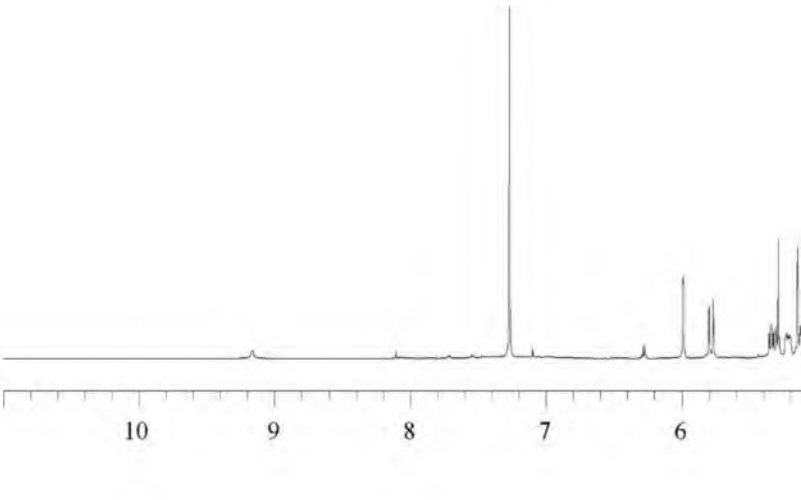


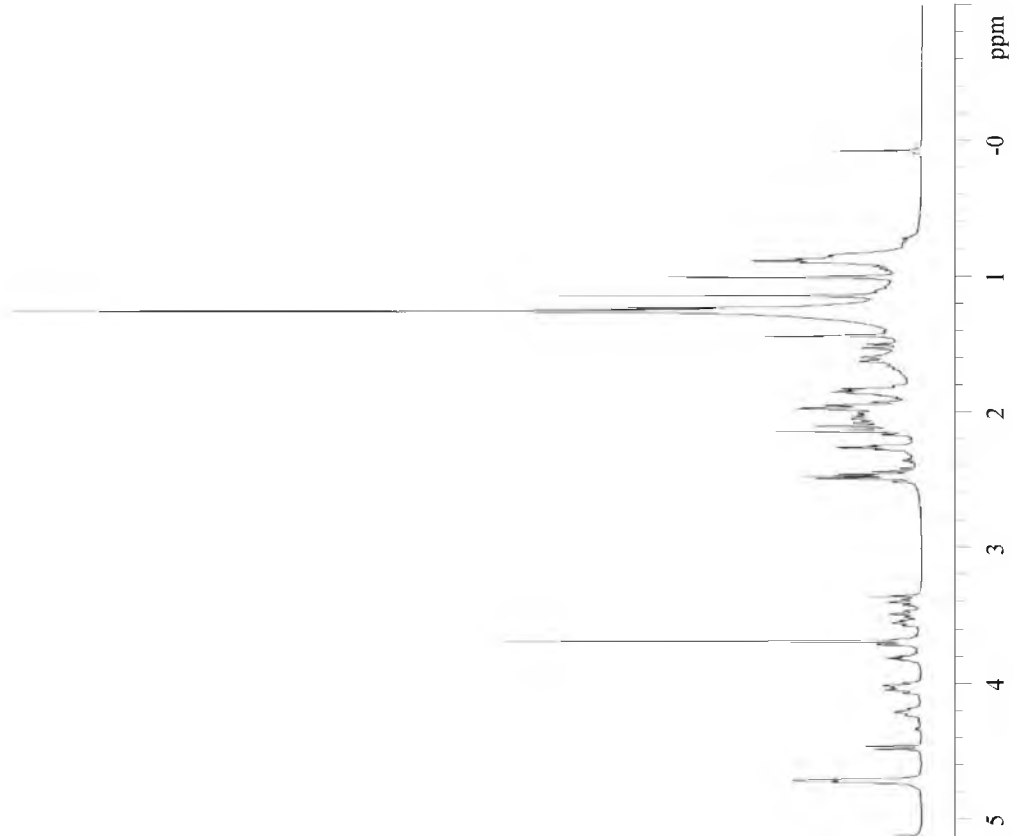
2.52
DEPT NMR (125 MHz, $CDCl_3$)



2.46

^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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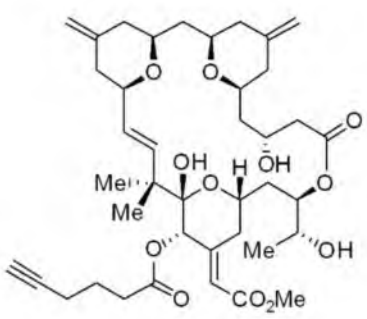
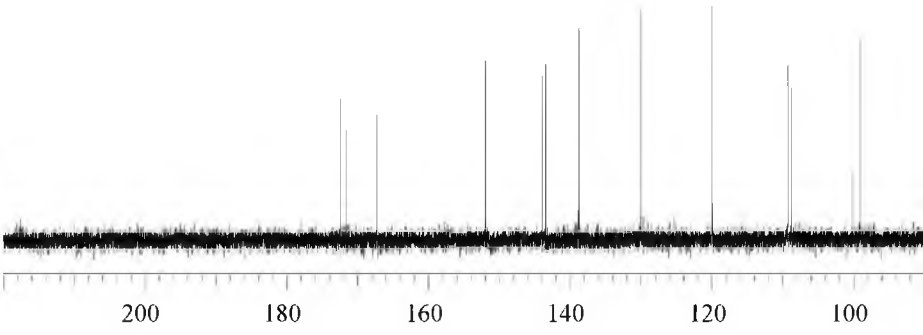


2.46
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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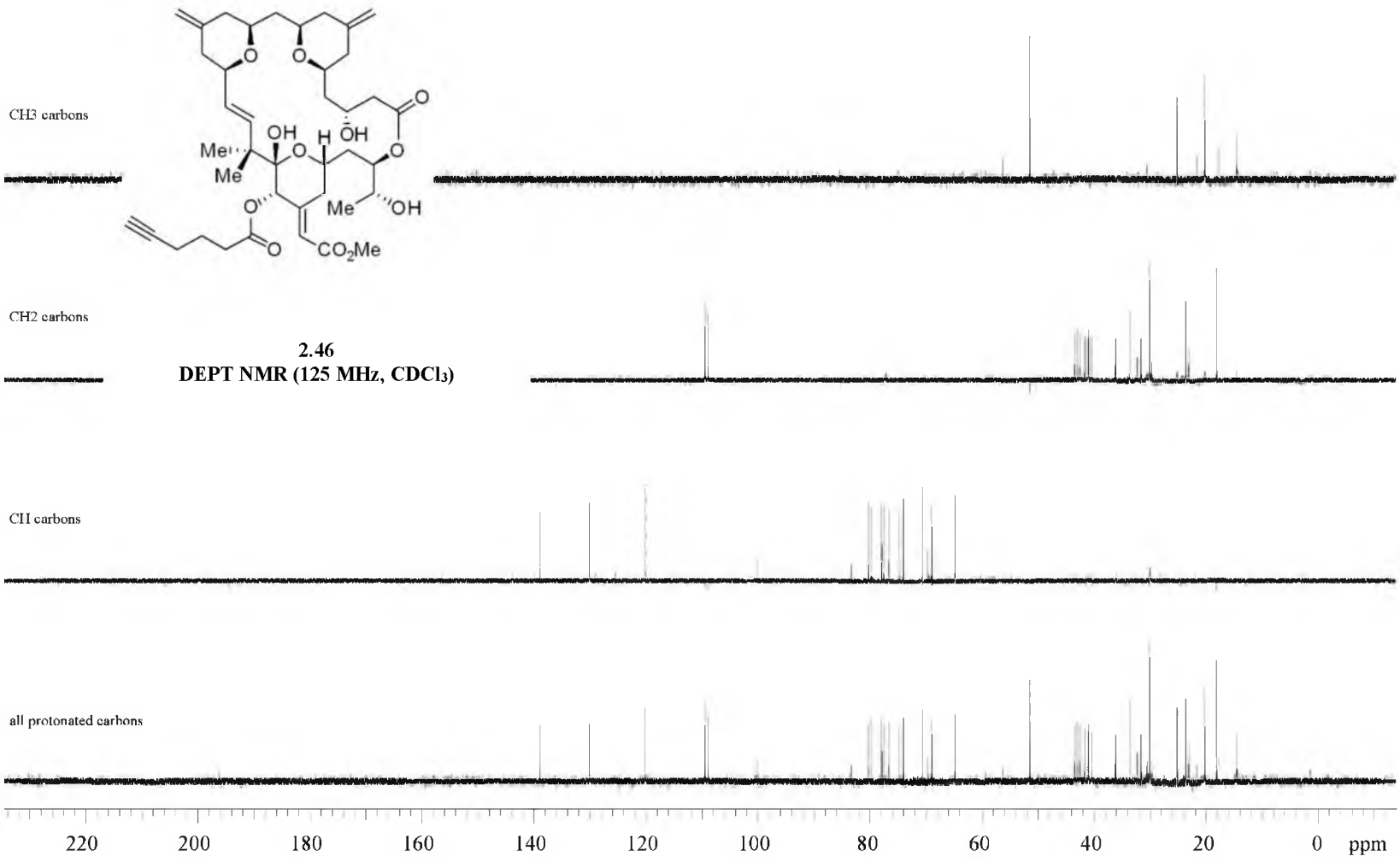
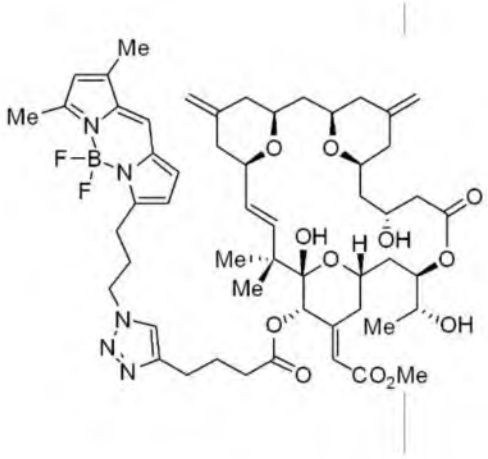
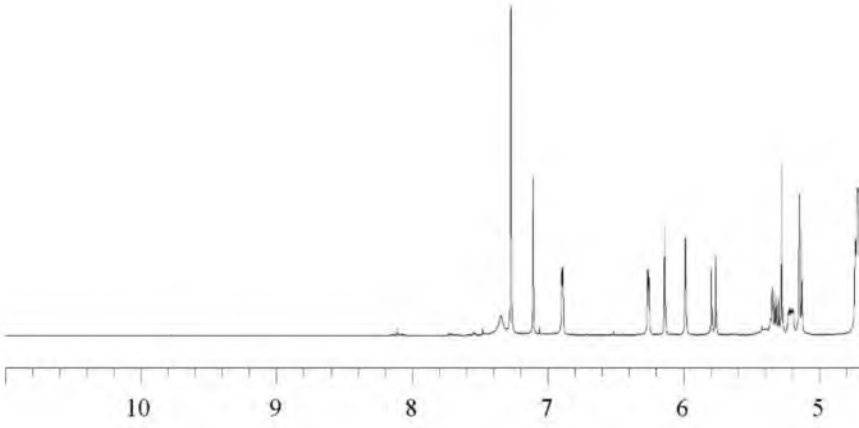
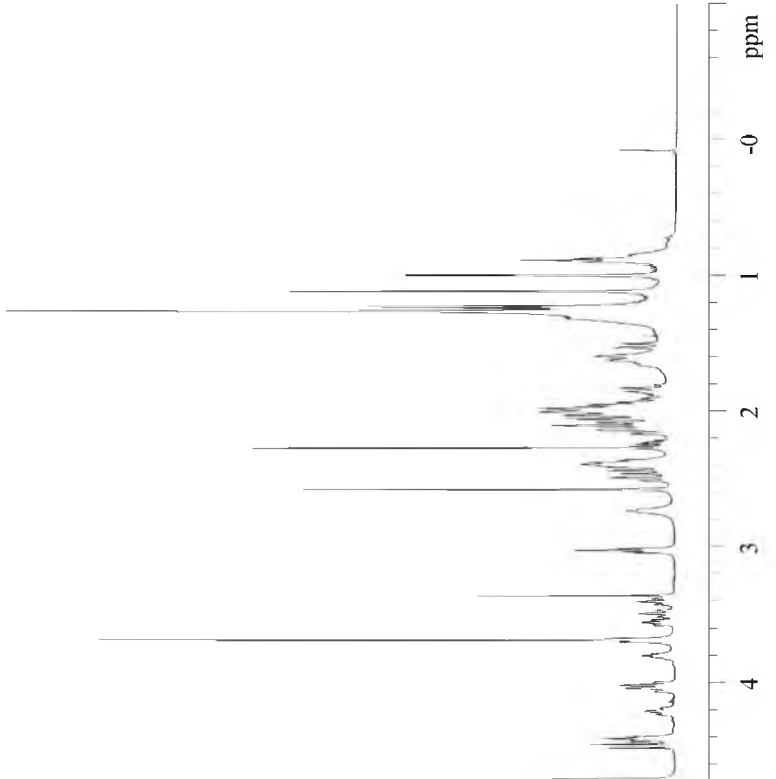


2.46
DEPT NMR (125 MHz, $CDCl_3$)



Merle 44
^{1}H NMR (500 MHz, $CDCl_3$)

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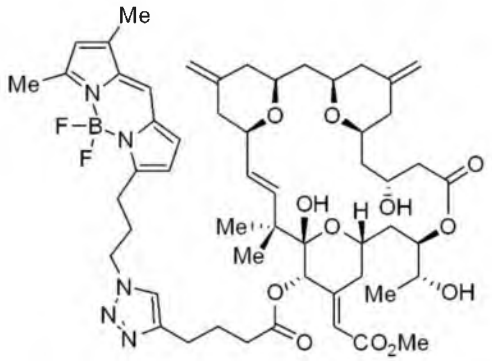
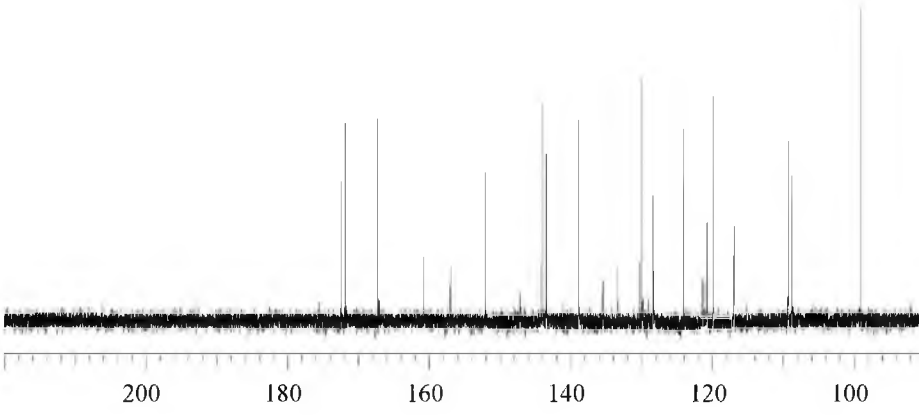


Merle 44
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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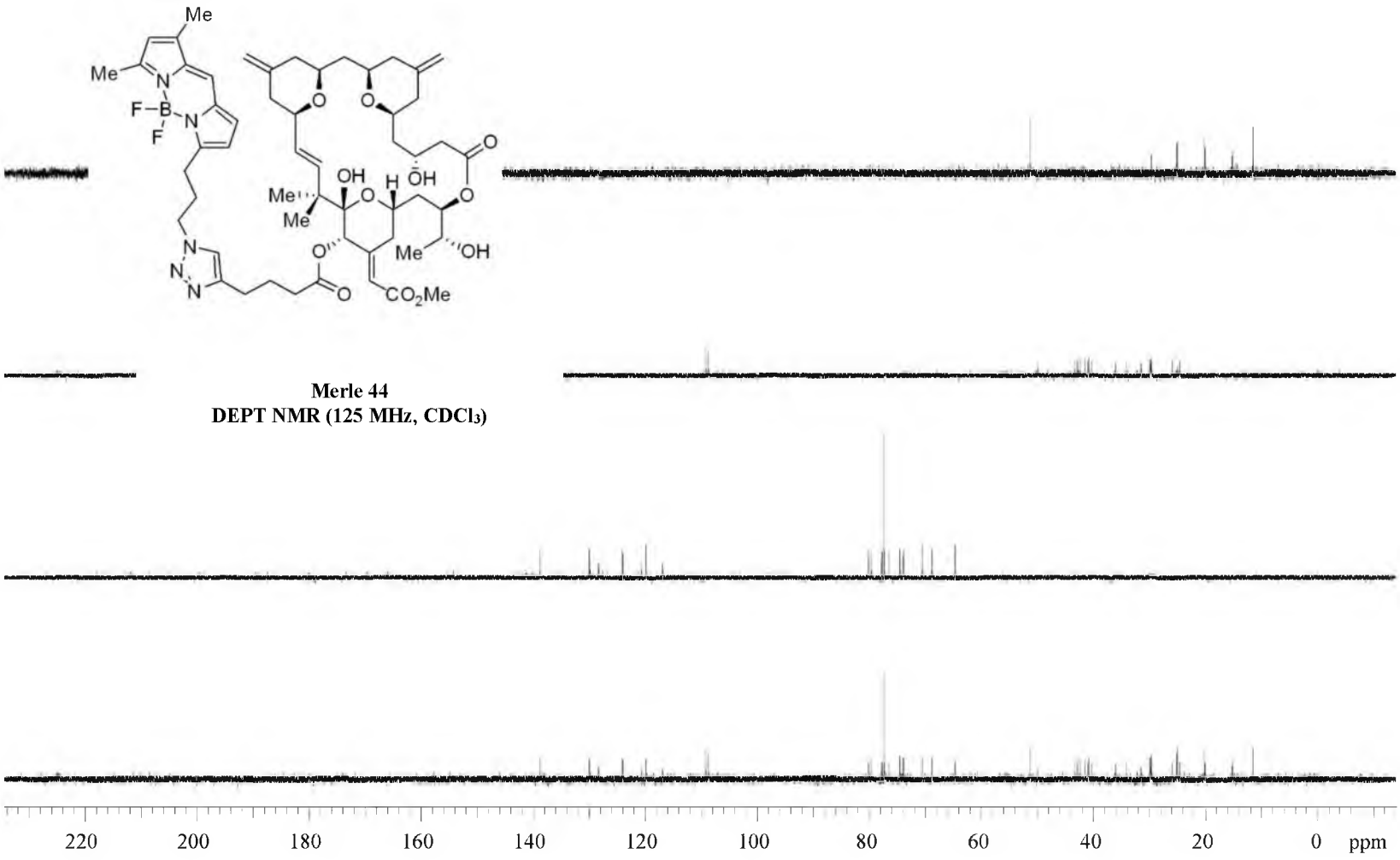
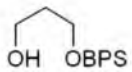
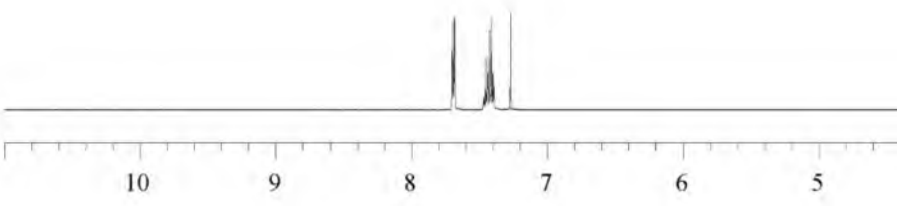
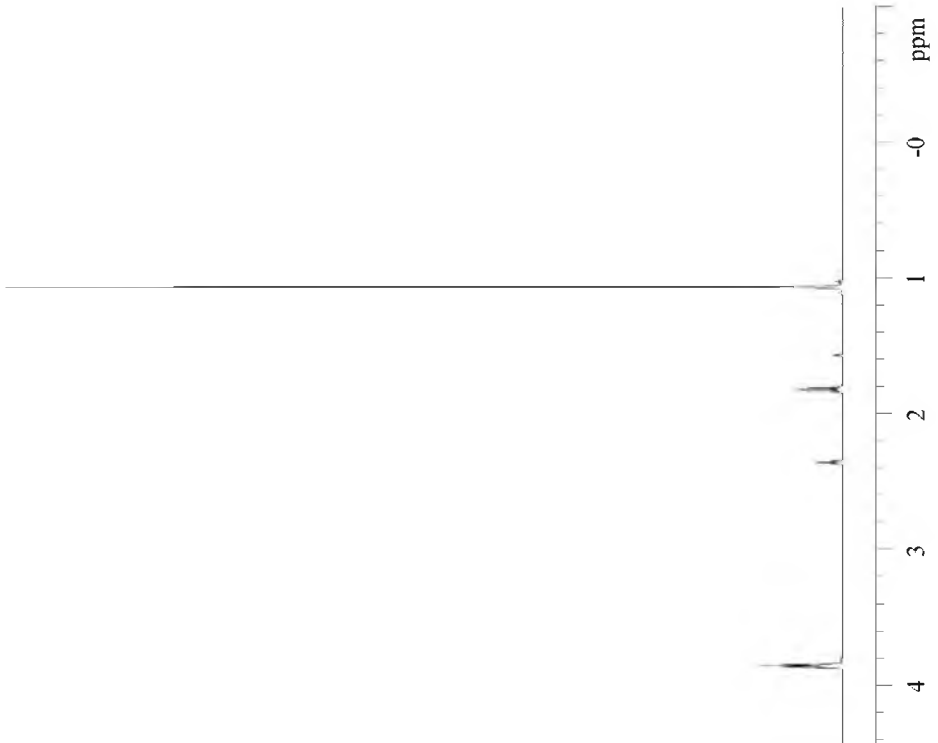


Merle 44
DEPT NMR (125 MHz, $CDCl_3$)



2.16.1
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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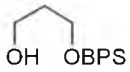
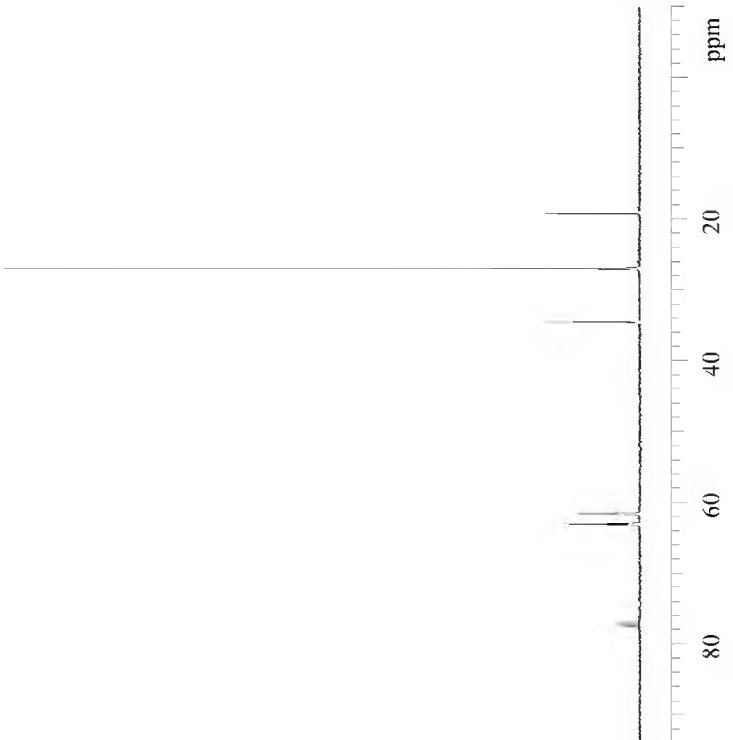
3
4



2.16.1
^{13}C NMR (125 MHz, $CDCl_3$)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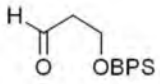
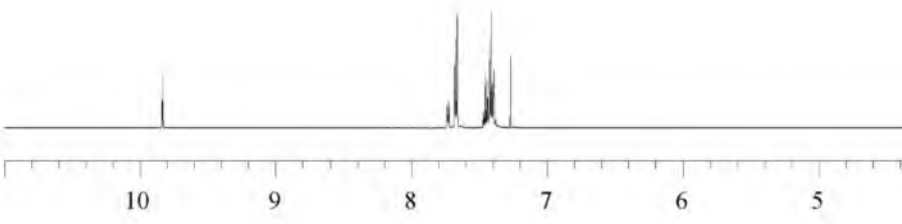


2.16.2
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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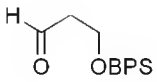

2.16.2
^{13}C NMR (125 MHz, $CDCl_3$)


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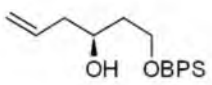
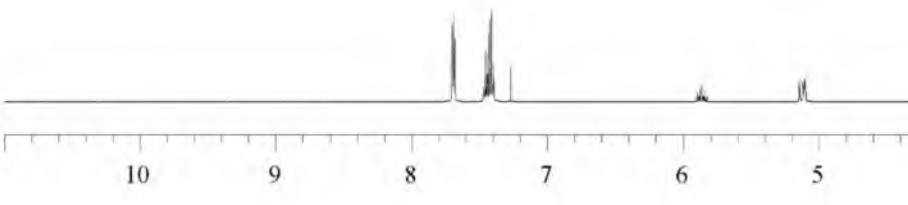


2.16.3
^{1}H NMR (500 MHz, $CDCl_3$)

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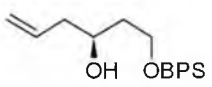
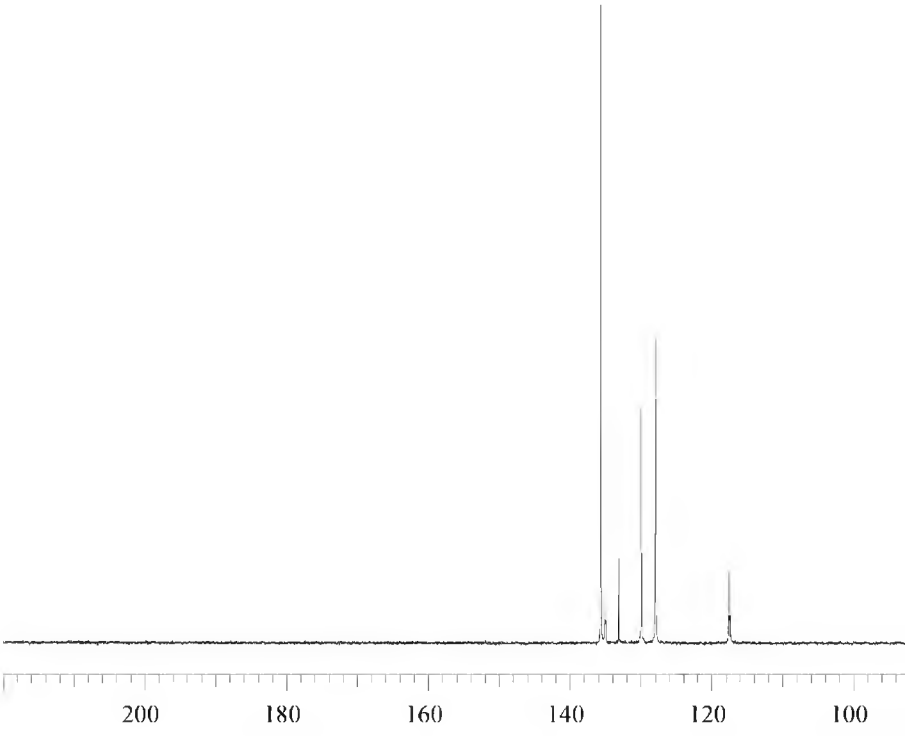


2.16.3
^{13}C NMR (125 MHz, $CDCl_3$)

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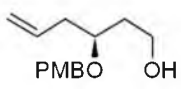
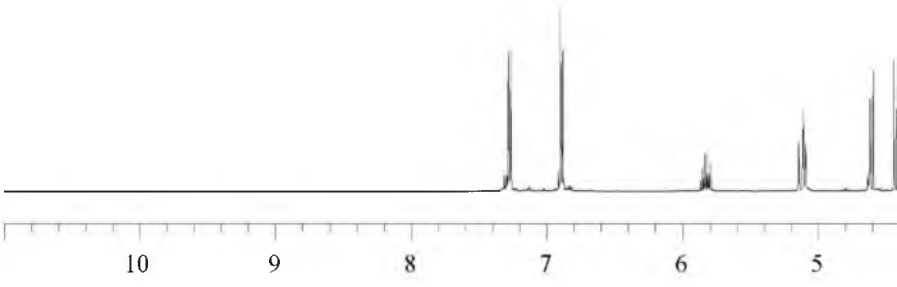
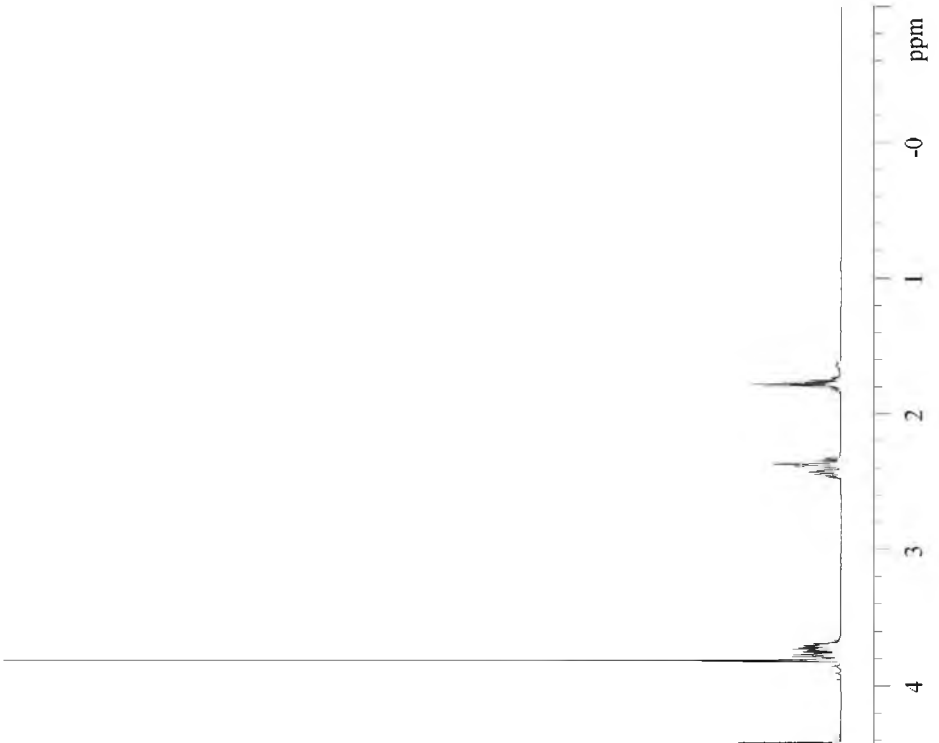


2.16.4
^{1}H NMR (500 MHz, $CDCl_3$)

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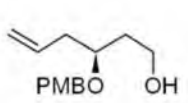
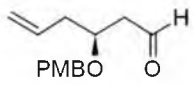
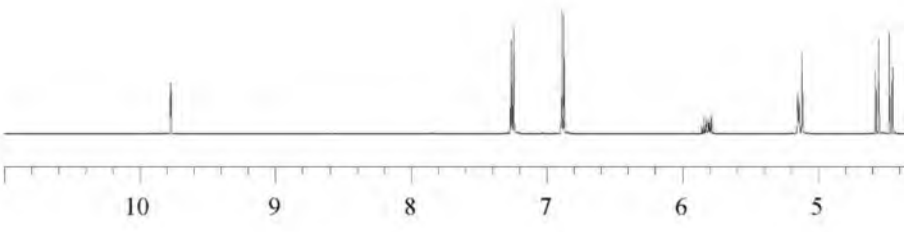


2.16.4
^{13}C NMR (125 MHz, $CDCl_3$)



2.16.5
^{1}H NMR (500 MHz, $CDCl_3$)

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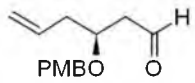
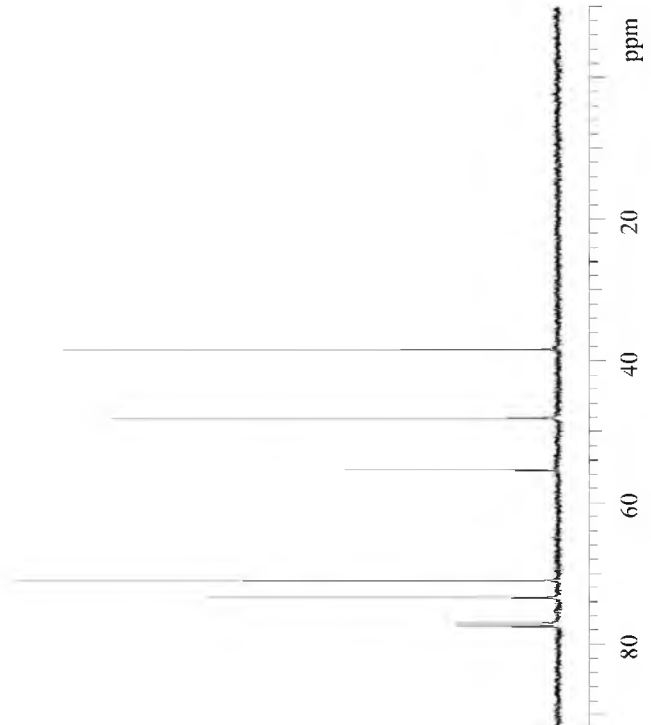


2.16.5
^{13}C NMR (125 MHz, $CDCl_3$)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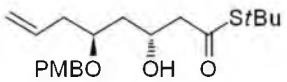
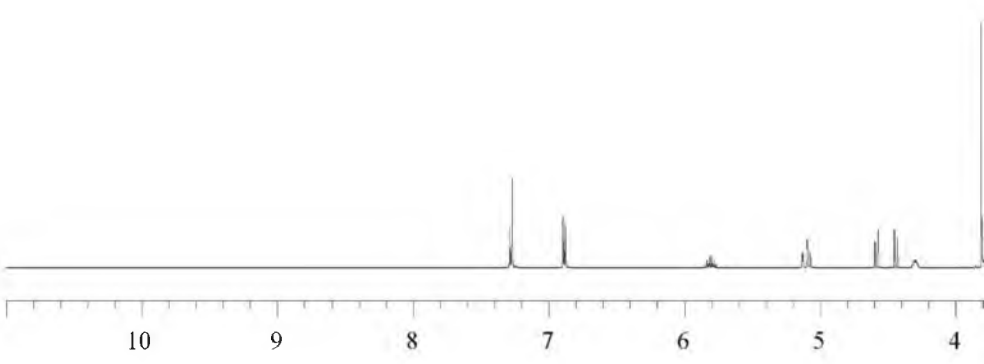


2.16.6
^{1}H NMR (500 MHz, $CDCl_3$)

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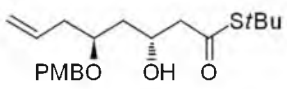
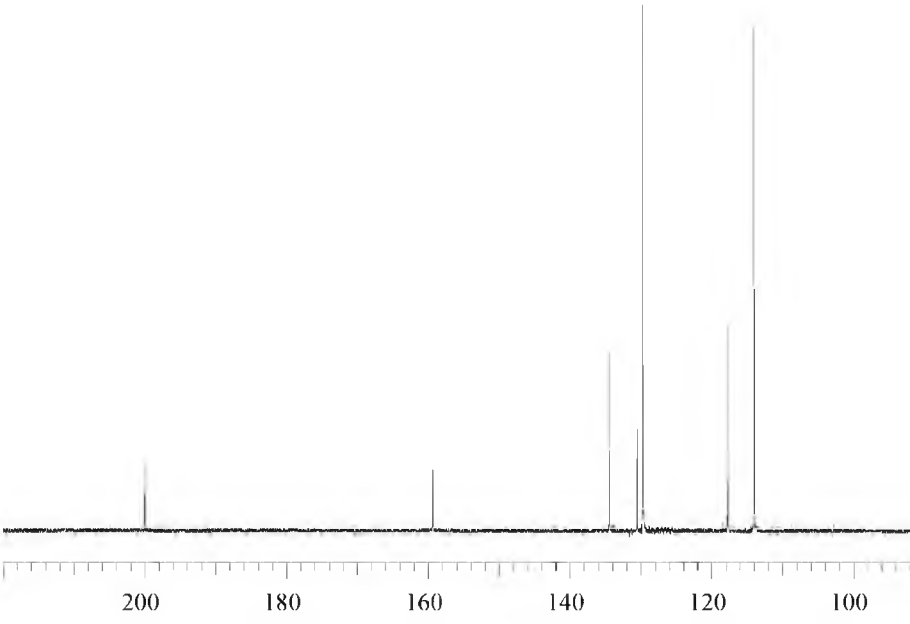


2.16.6
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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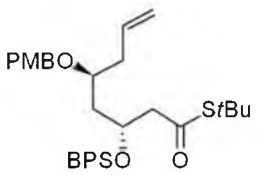
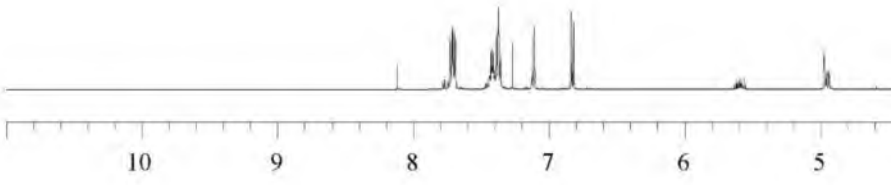
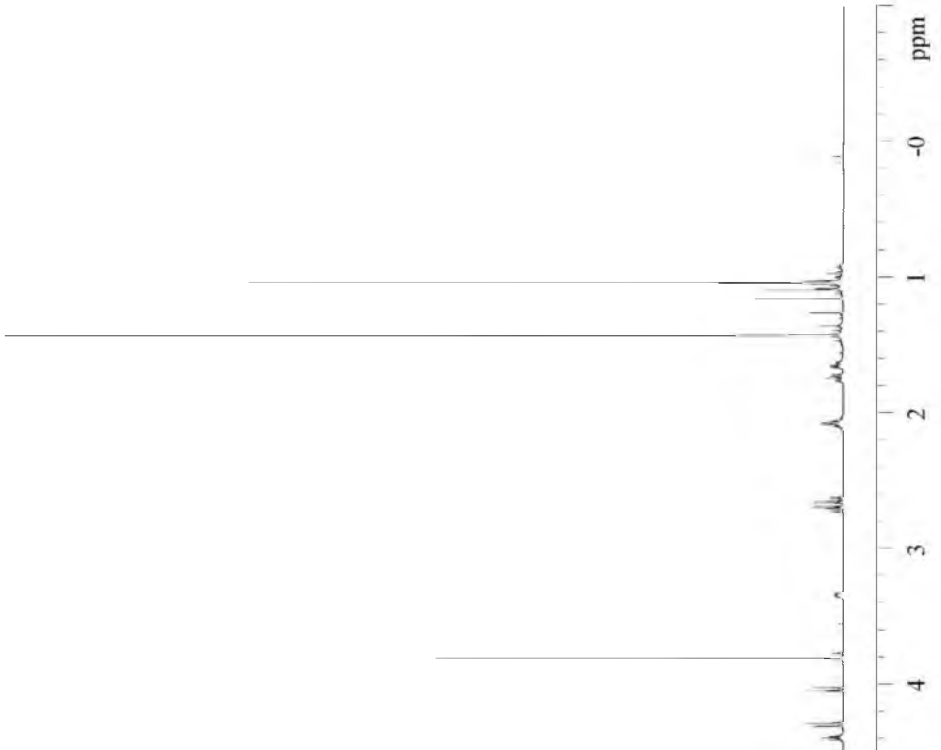


2.16.7
^{1}H NMR (500 MHz, $CDCl_3$)

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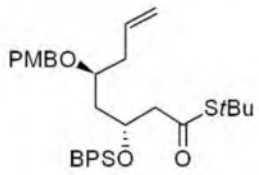
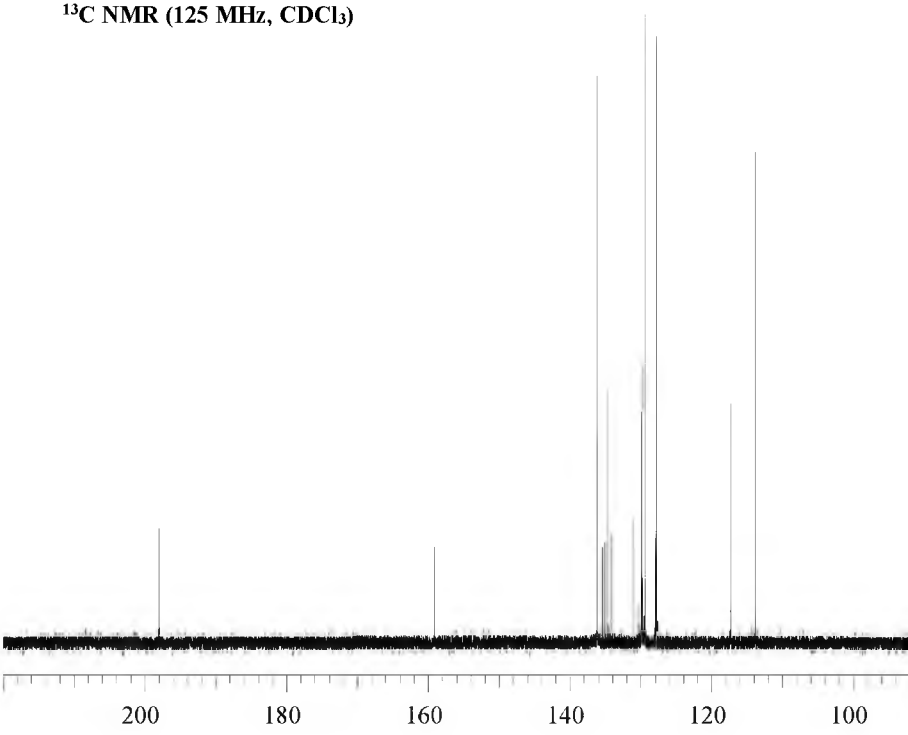


2.16.7
^{13}C NMR (125 MHz, $CDCl_3$)

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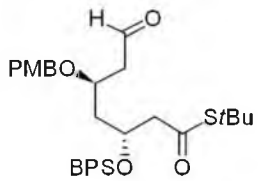
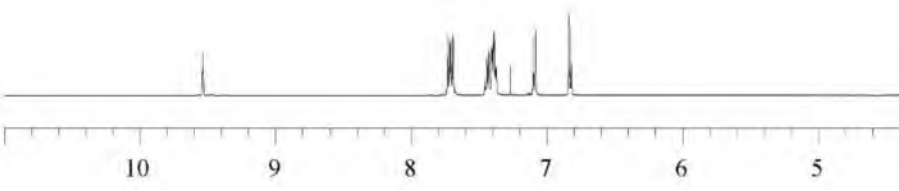


2.16.8
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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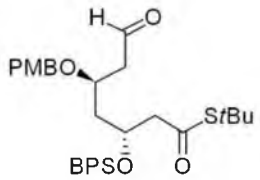
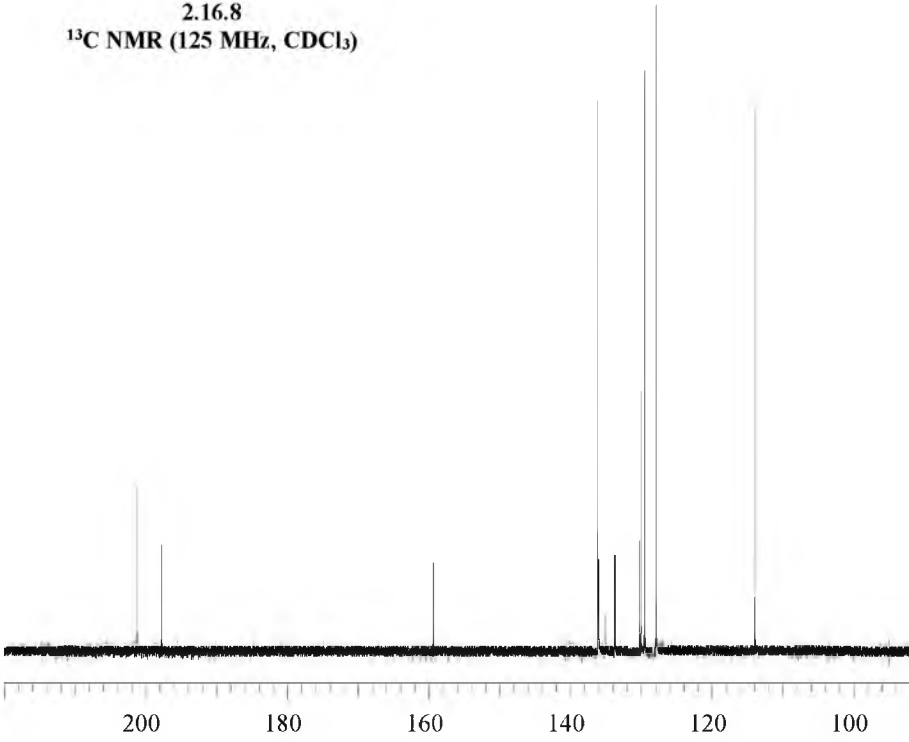


2.16.8
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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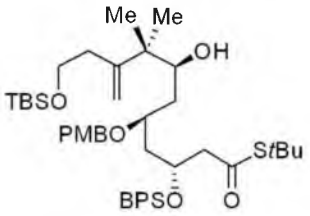
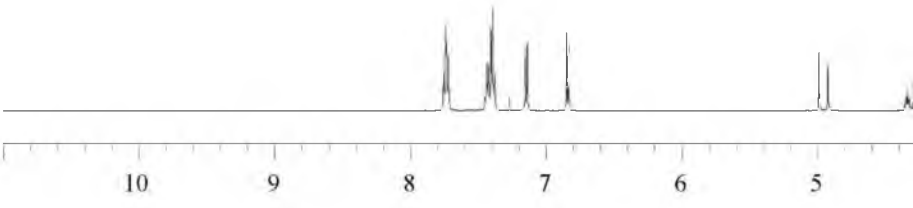


2.16.9
^{1}H NMR (500 MHz, $CDCl_3$)

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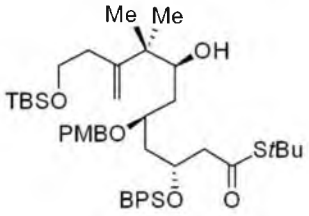
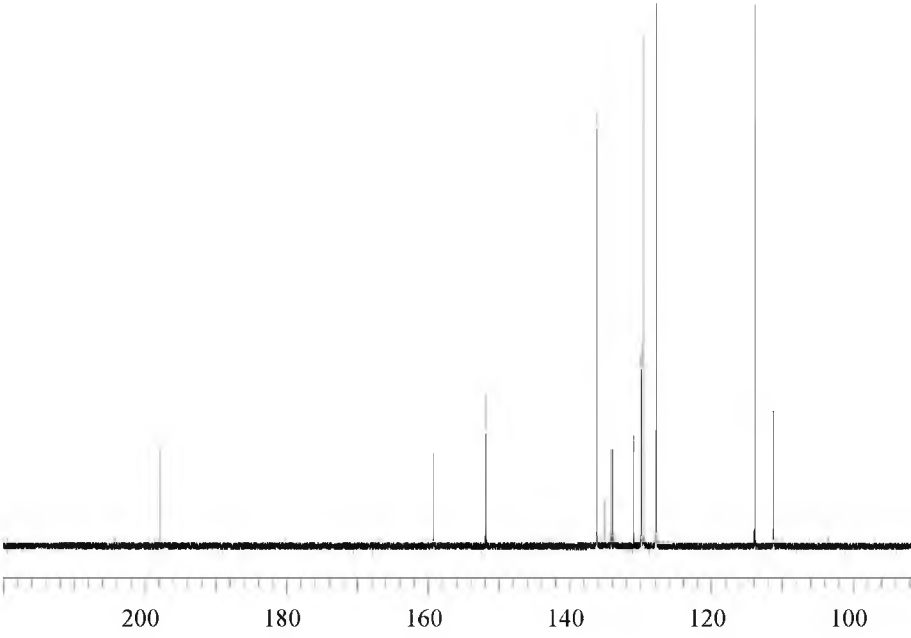


2.16.9
^{13}C NMR (125 MHz, $CDCl_3$)

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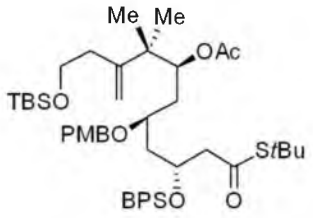
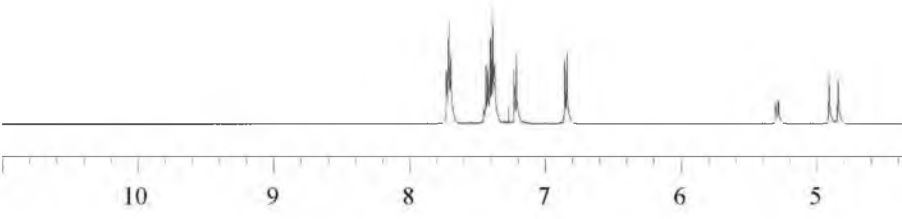


2.16.10
^{1}H NMR (500 MHz, $CDCl_3$)

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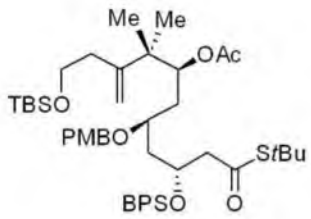
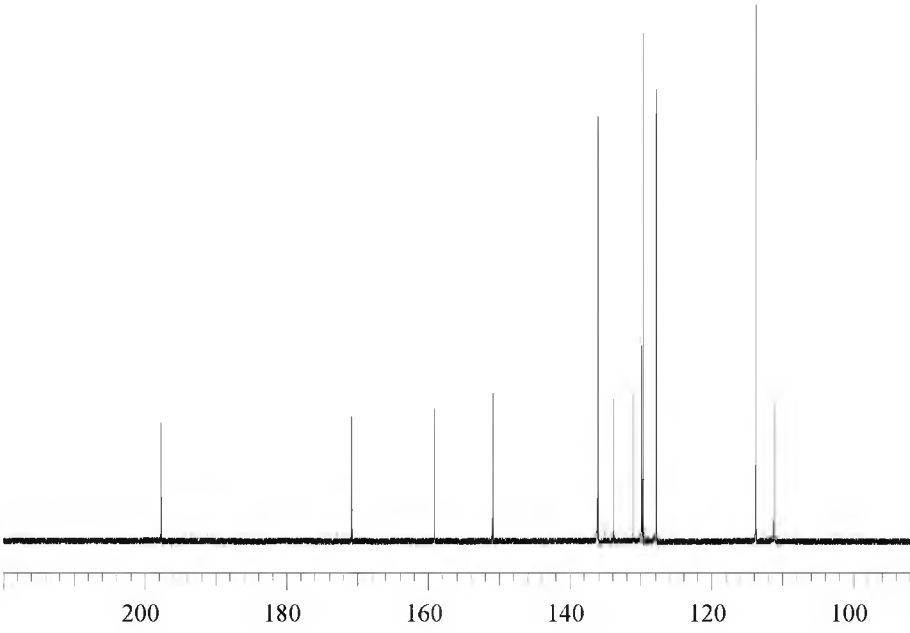


2.16.10
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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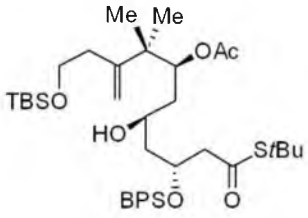
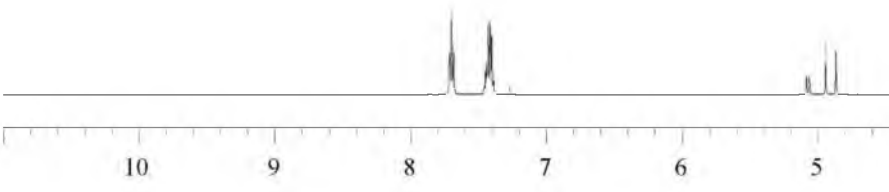
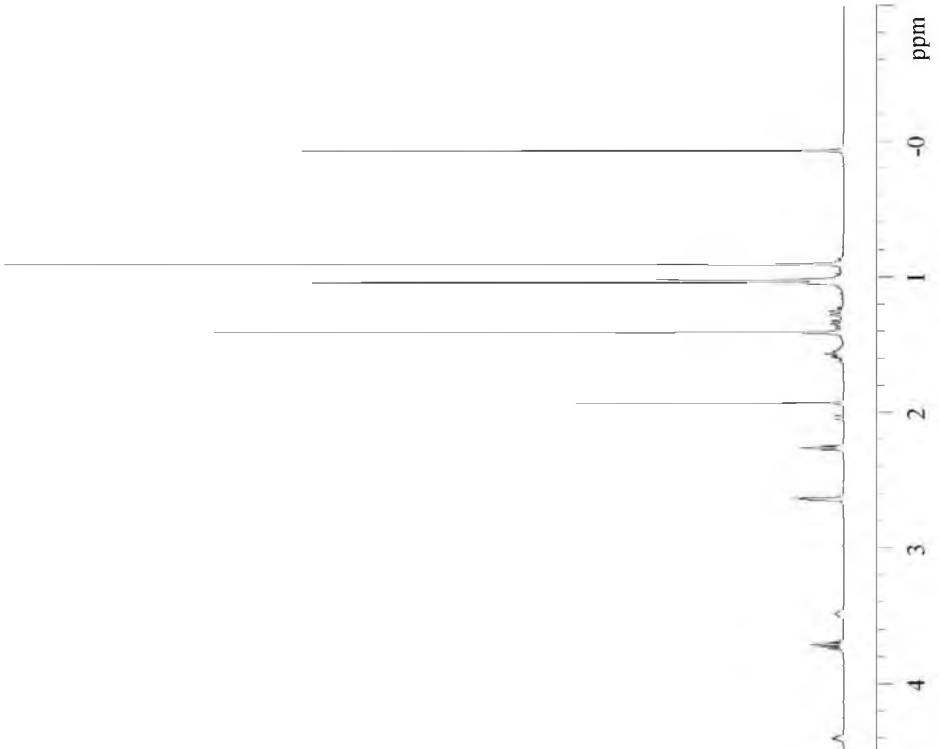


2.16.11
^{1}H NMR (500 MHz, $CDCl_3$)

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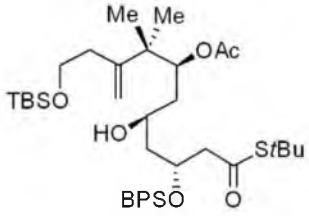
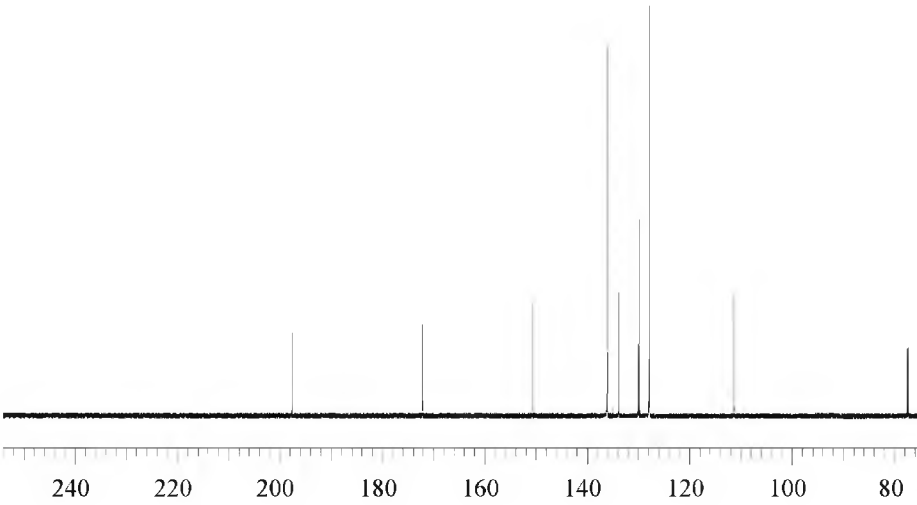


2.16.11
^{13}C NMR (125 MHz, $CDCl_3$)

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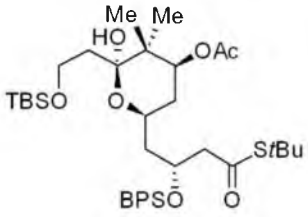
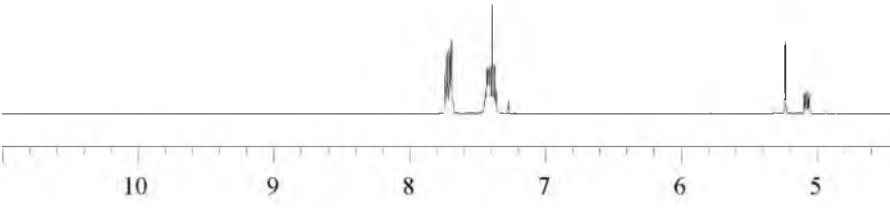
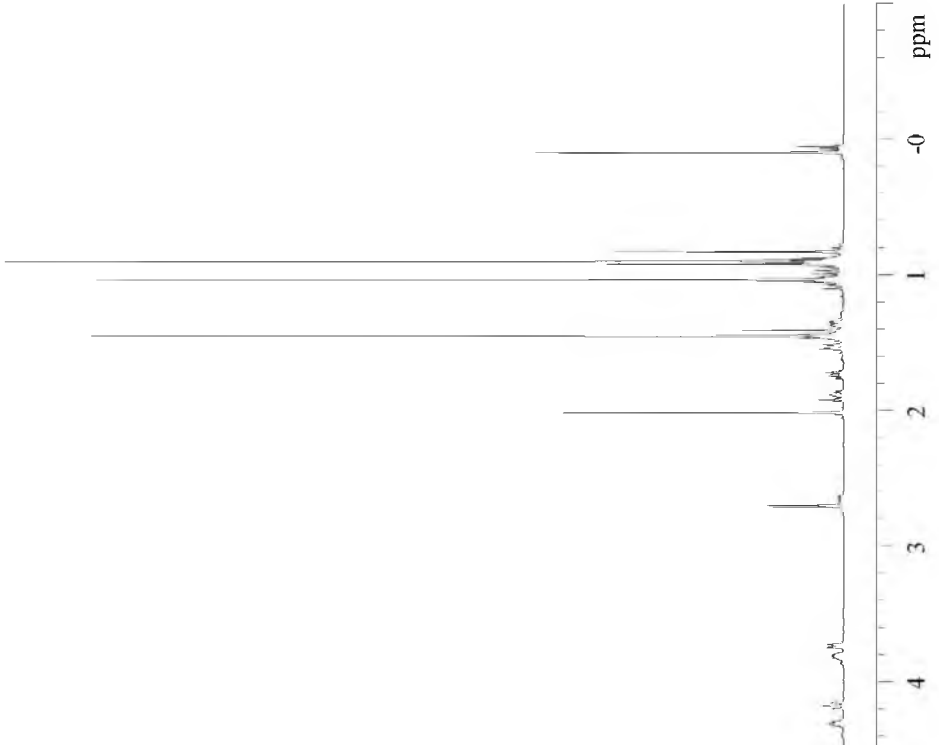


2.16.12
^{1}H NMR (500 MHz, $CDCl_3$)

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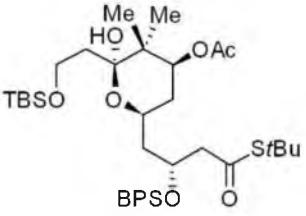
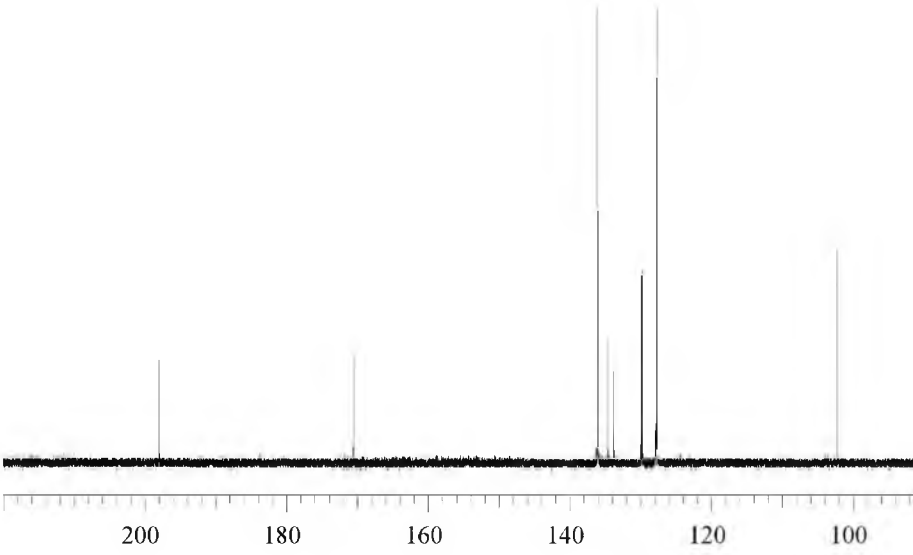
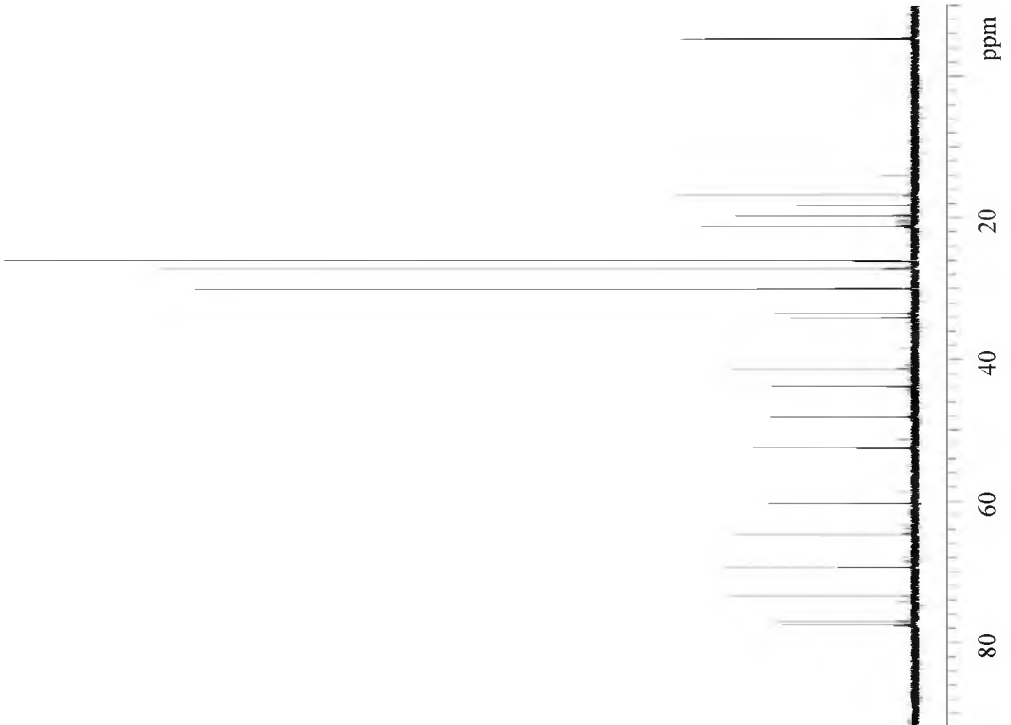


2.16.12
^{13}C NMR (125 MHz, $CDCl_3$)

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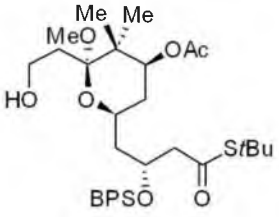
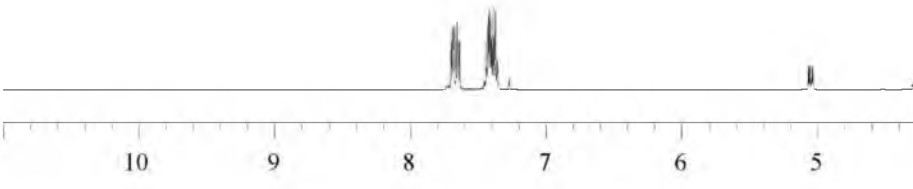
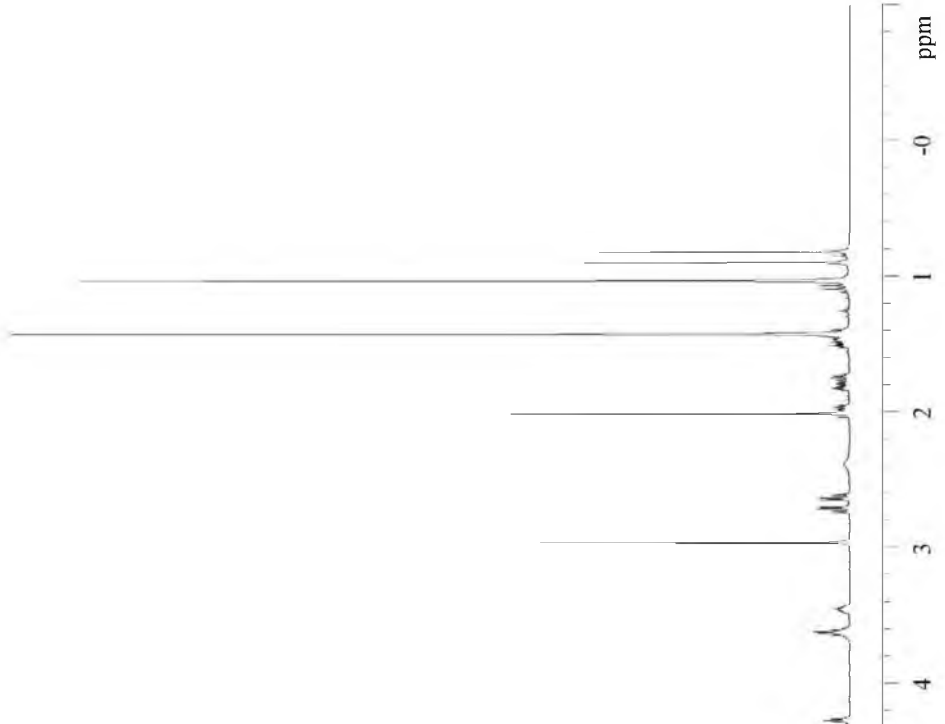


2.16.13
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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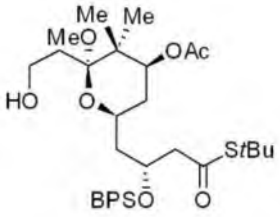
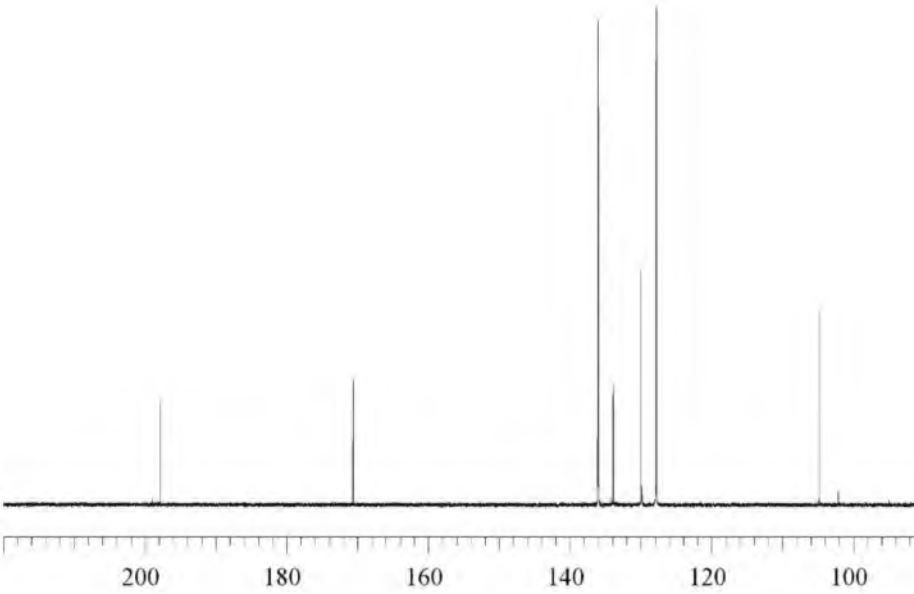


2.16.13
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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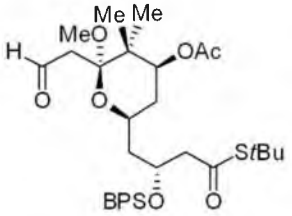
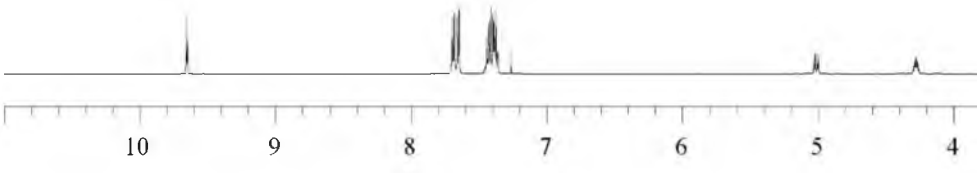
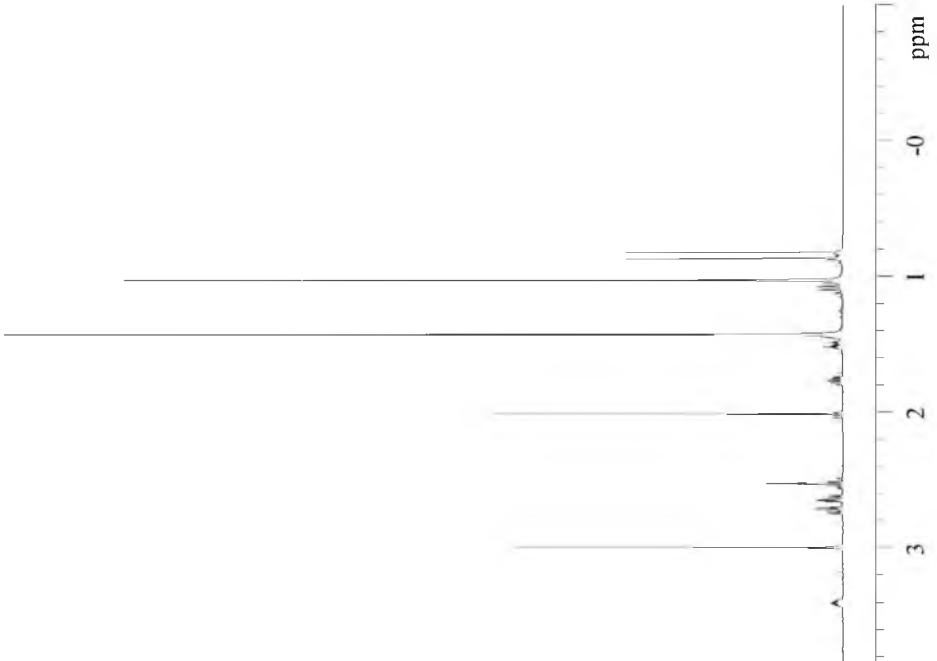


2.16

^{1}H NMR (500 MHz, $CDCl_3$)

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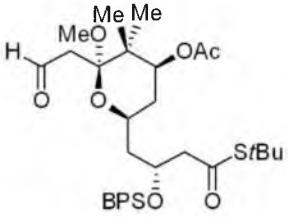
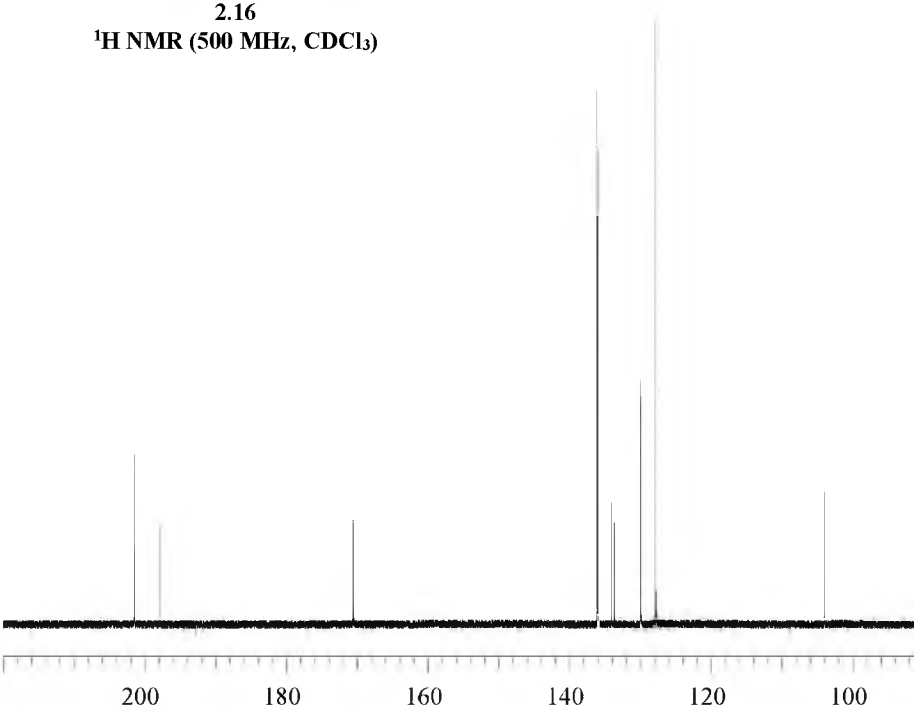


2.16
^{1}H NMR (500 MHz, $CDCl_3$)

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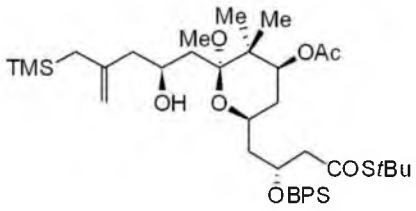
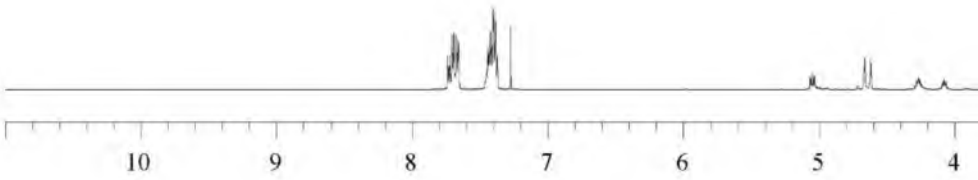


2.63
^{1}H NMR (500 MHz, $CDCl_3$)

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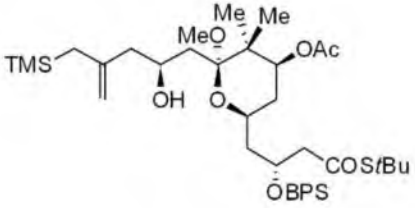
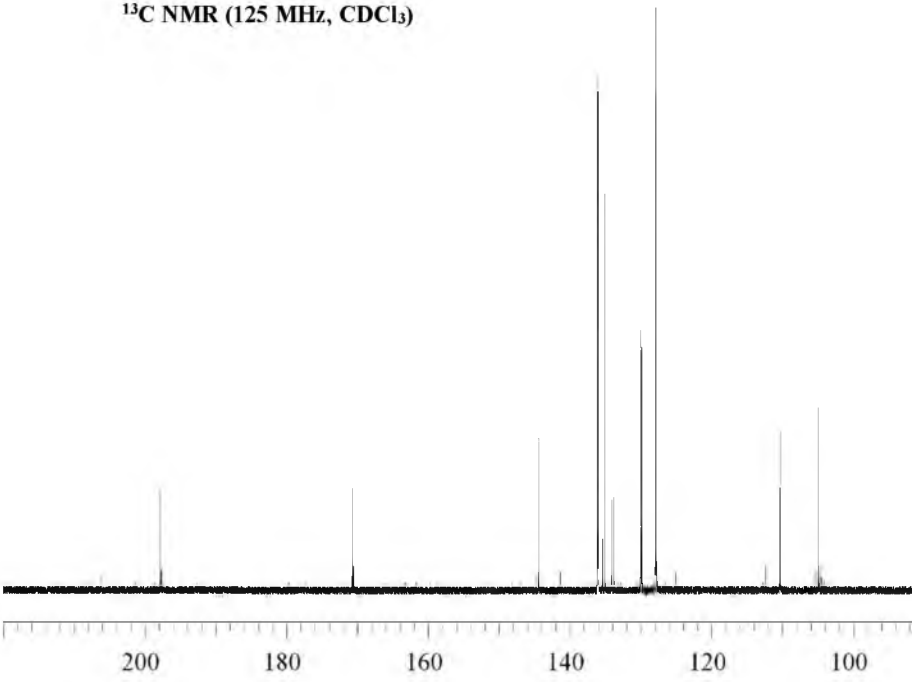


2.63

^{13}C NMR (125 MHz, $CDCl_3$)

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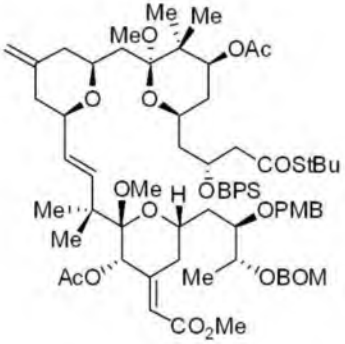
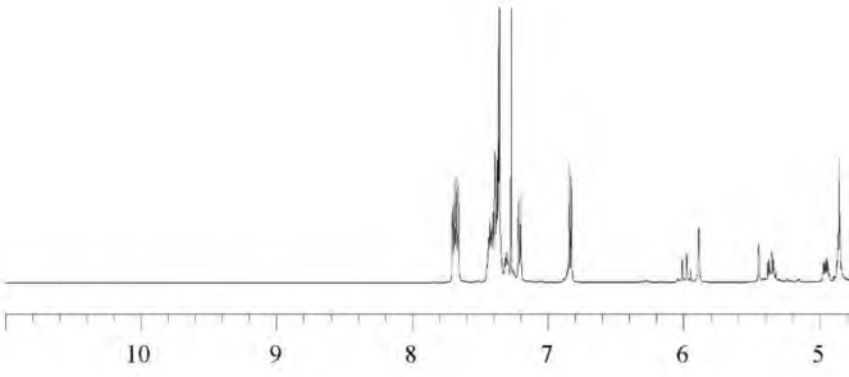
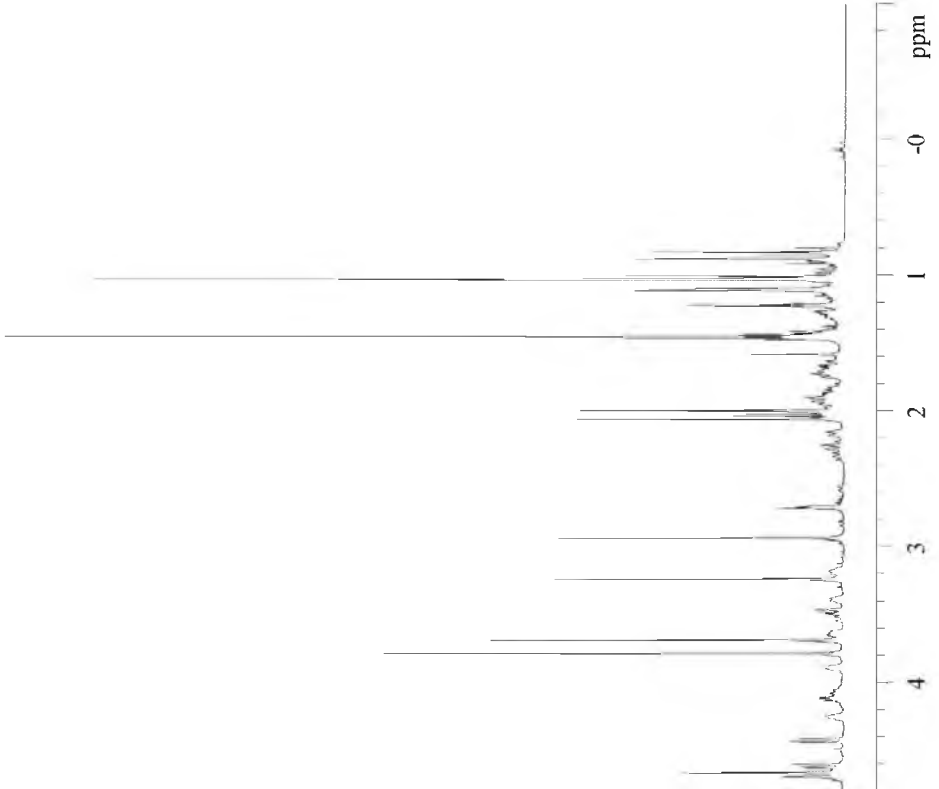


2.70

^{1}H NMR (500 MHz, $CDCl_3$)

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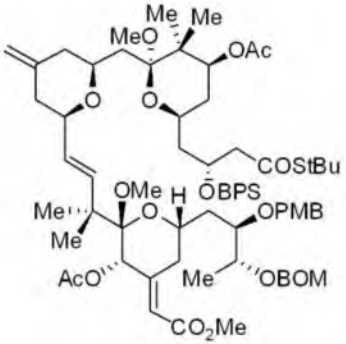
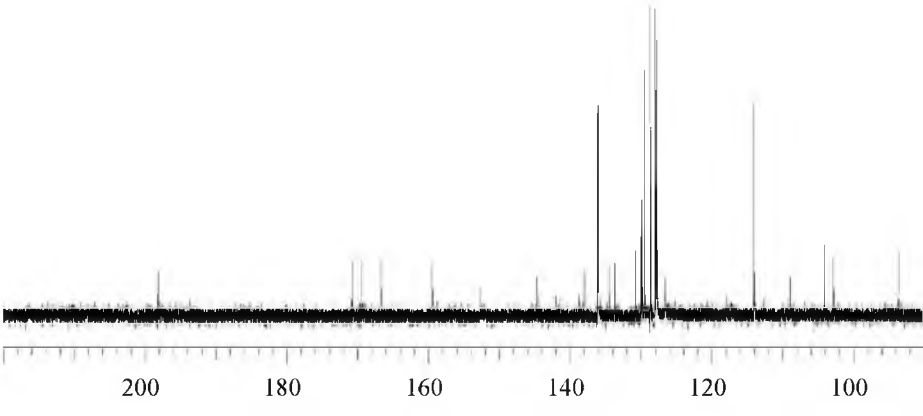


2.70

^{13}C NMR (125 MHz, $CDCl_3$)

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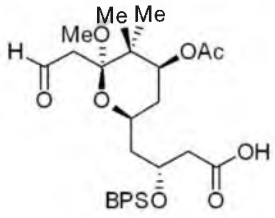
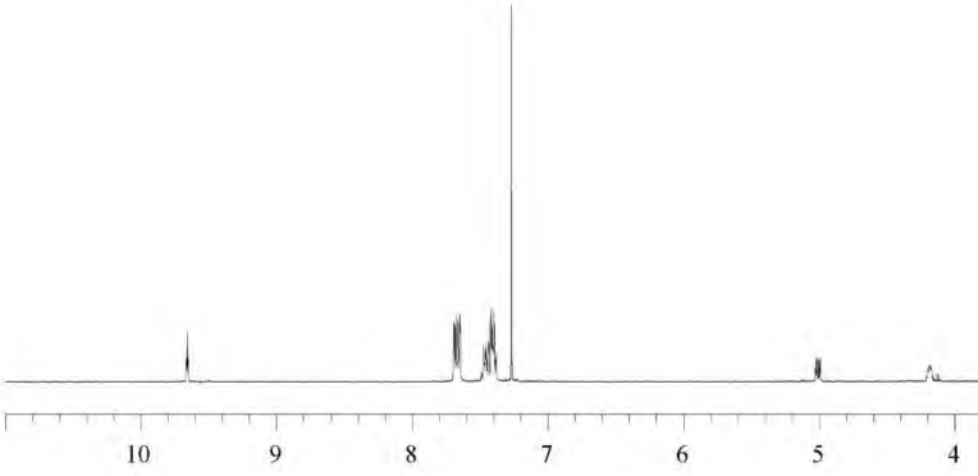


2.71
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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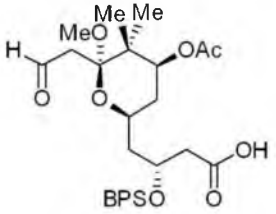
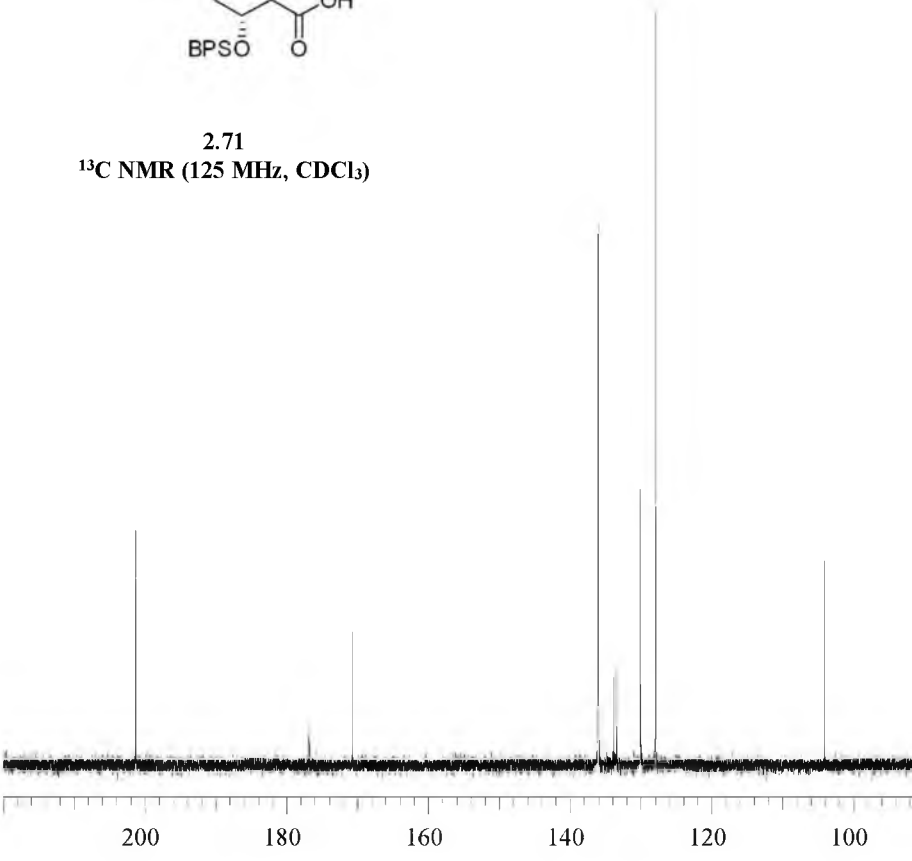


2.71
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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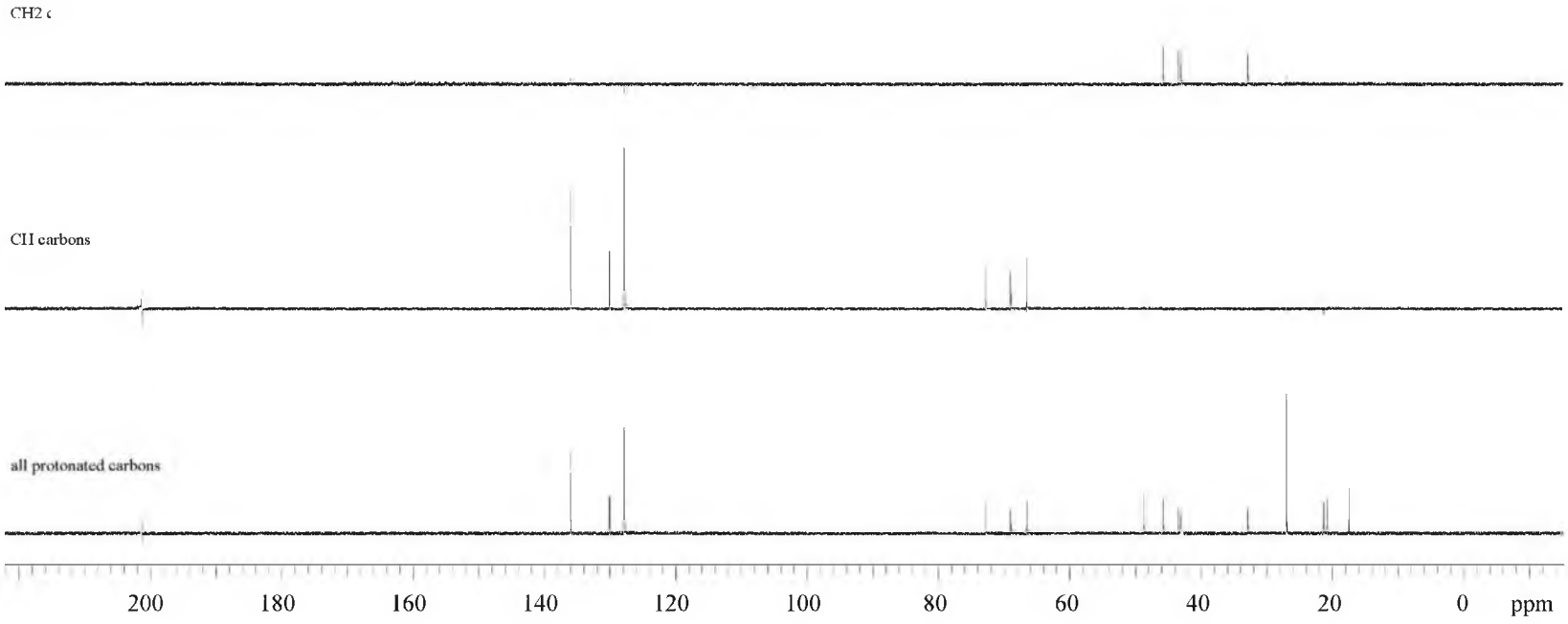
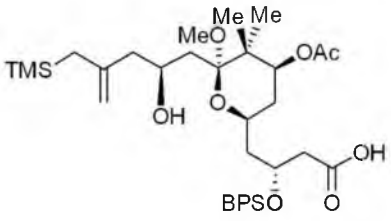
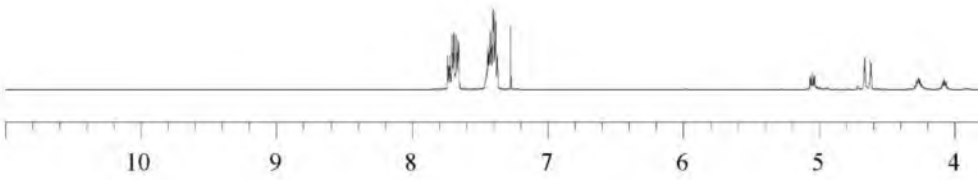
80

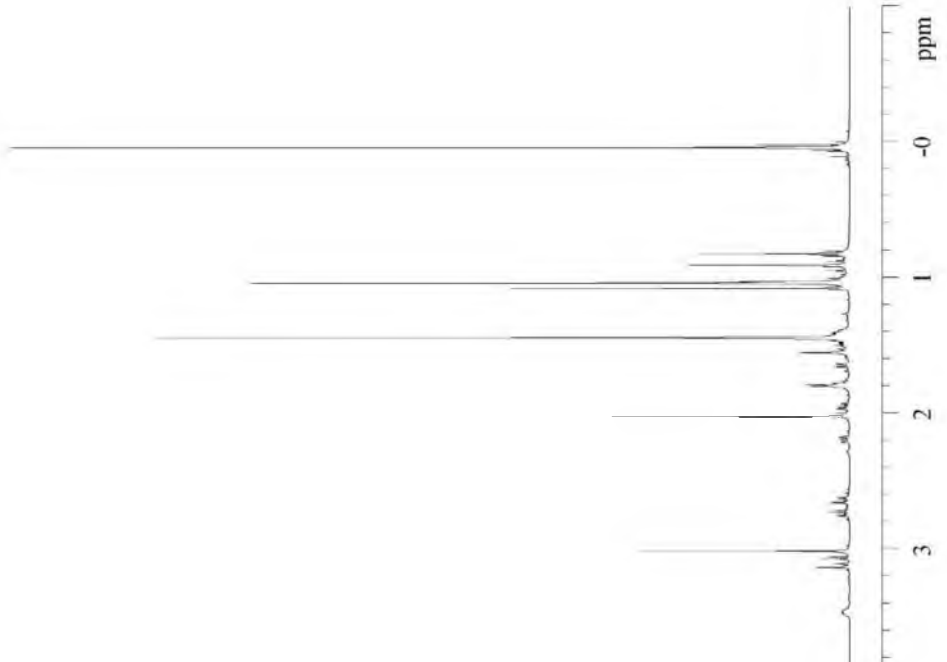
2.71
DEPT NMR (125 MHz, $CDCl_3$)





2.67
^{1}H NMR (500 MHz, $CDCl_3$)

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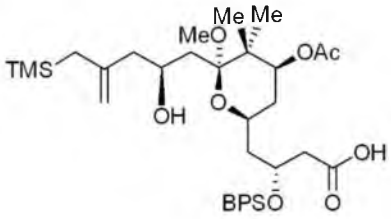
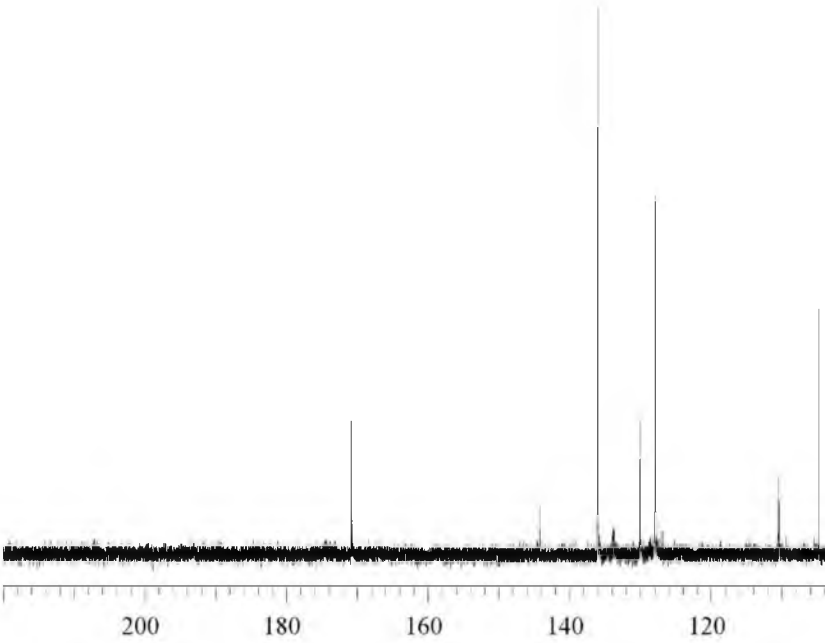
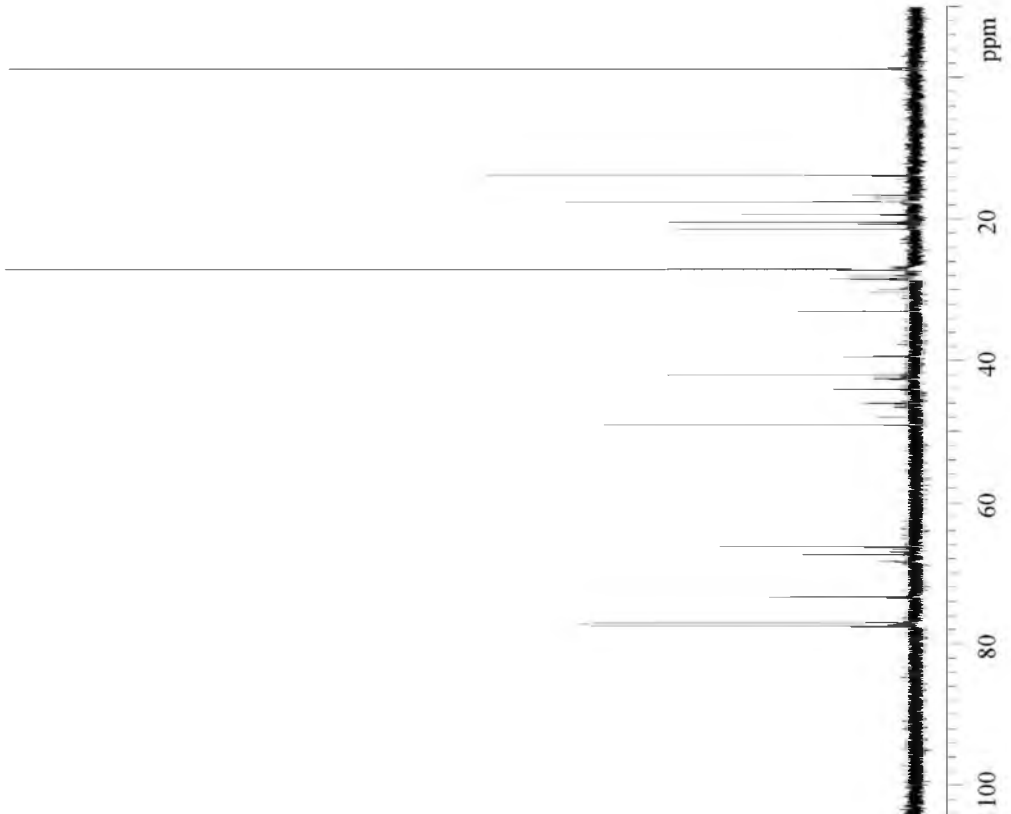


2.67

^{13}C NMR (125 MHz, $CDCl_3$)

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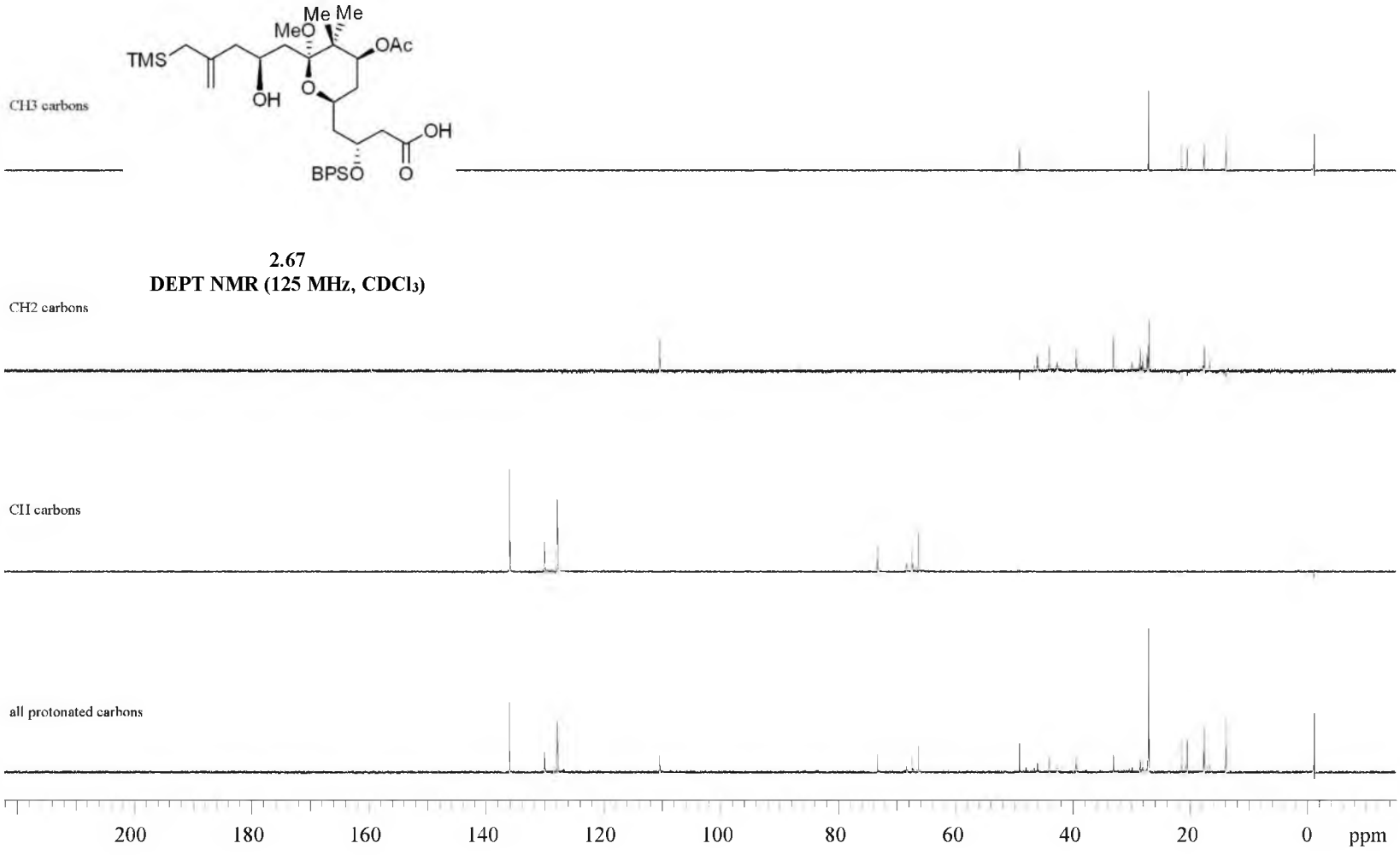
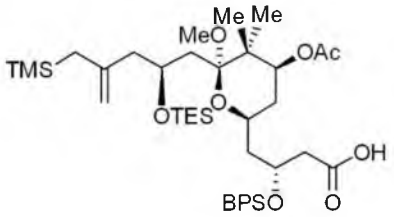
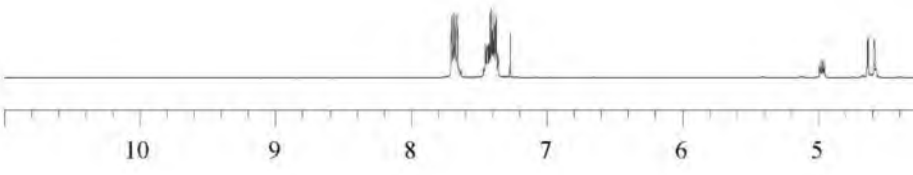
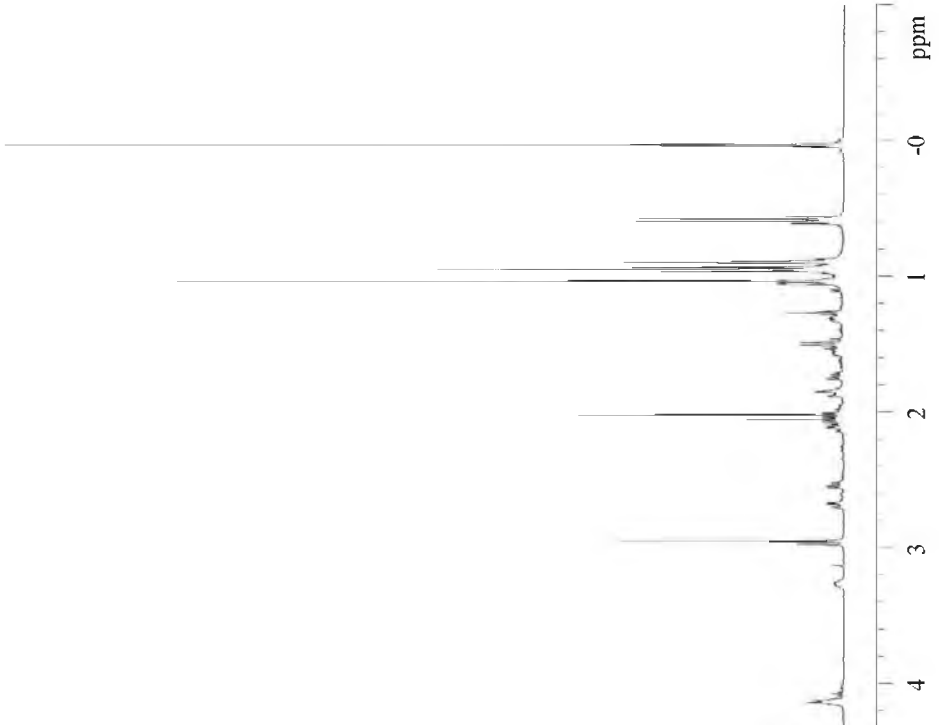


2.67
DEPT NMR (125 MHz, $CDCl_3$)



2.72
^{1}H NMR (500 MHz, $CDCl_3$)

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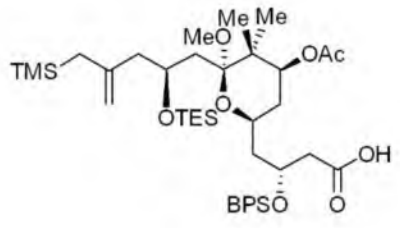
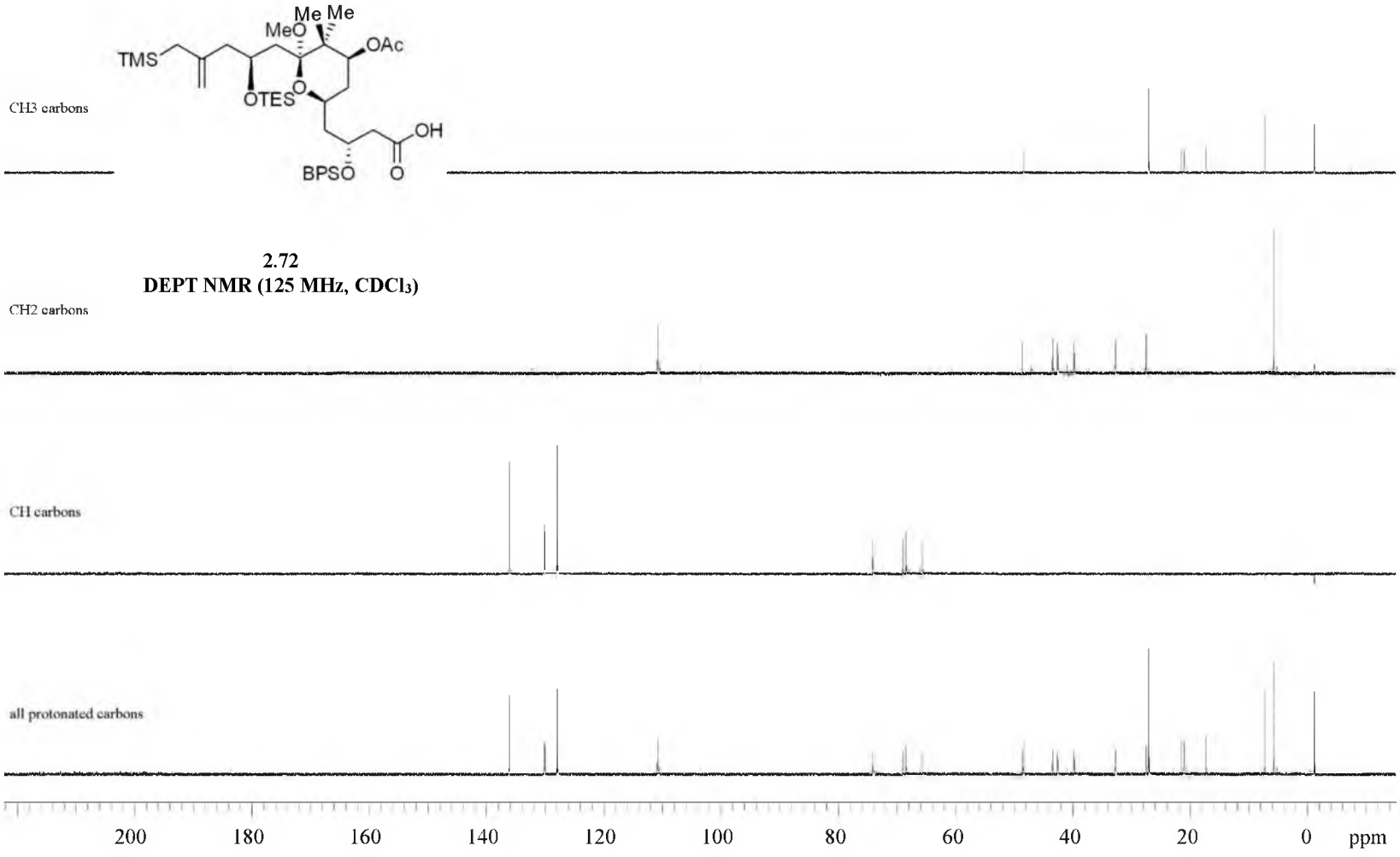
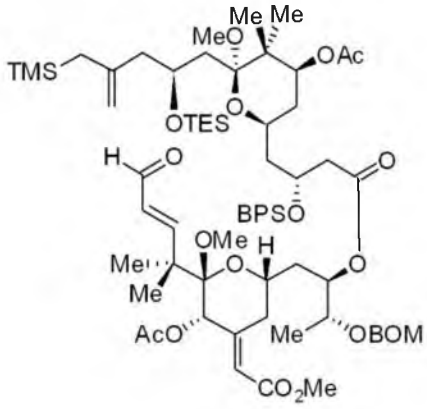


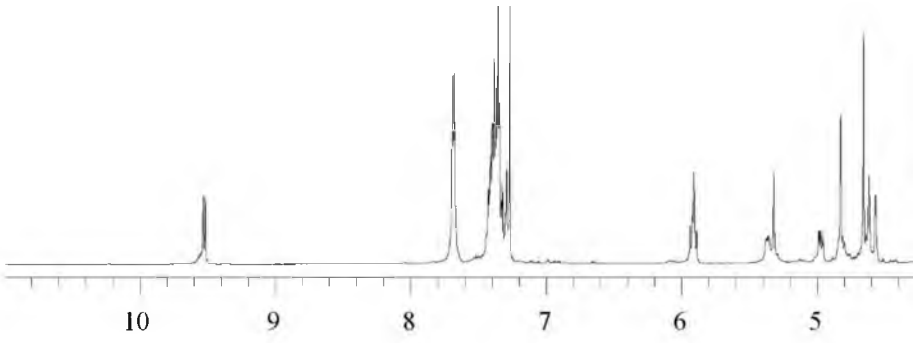
2.72
^{13}C NMR (125 MHz, $CDCl_3$)



2.72
DEPT NMR (125 MHz, $CDCl_3$)



2.73
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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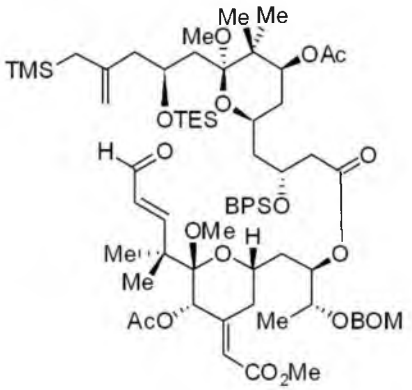
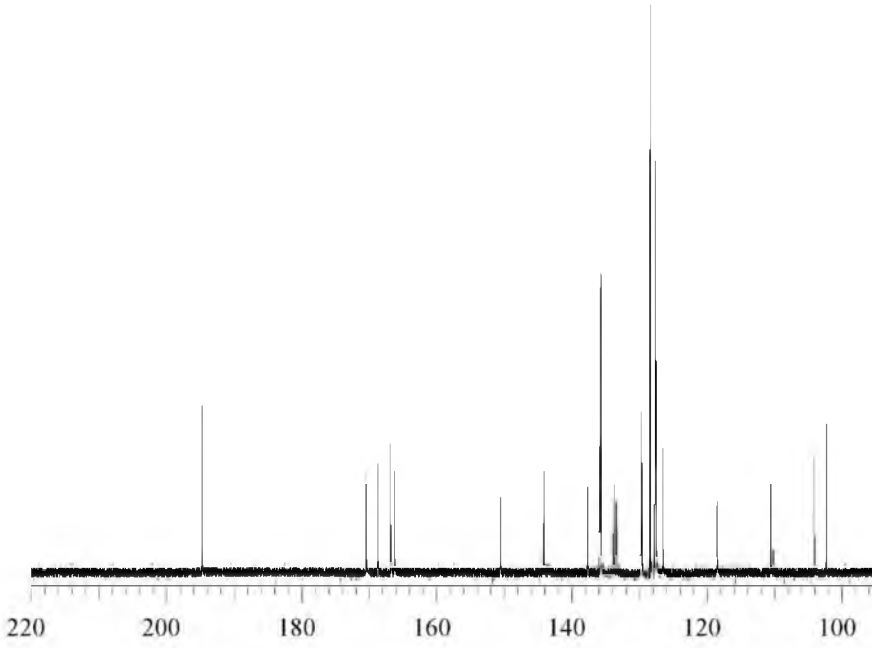


2.73

^{13}C NMR (125 MHz, $CDCl_3$)

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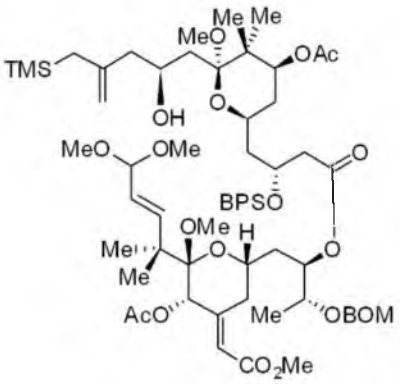
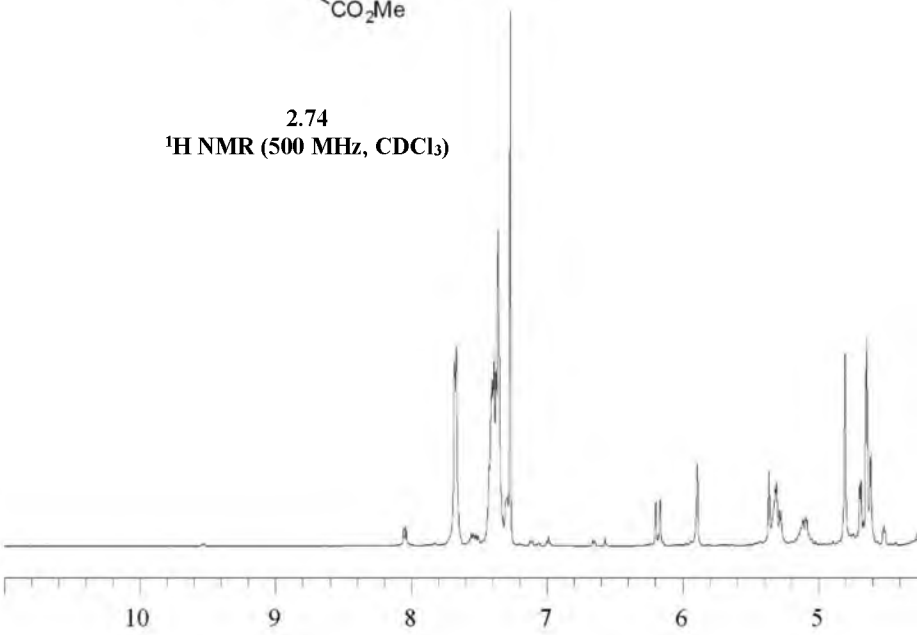
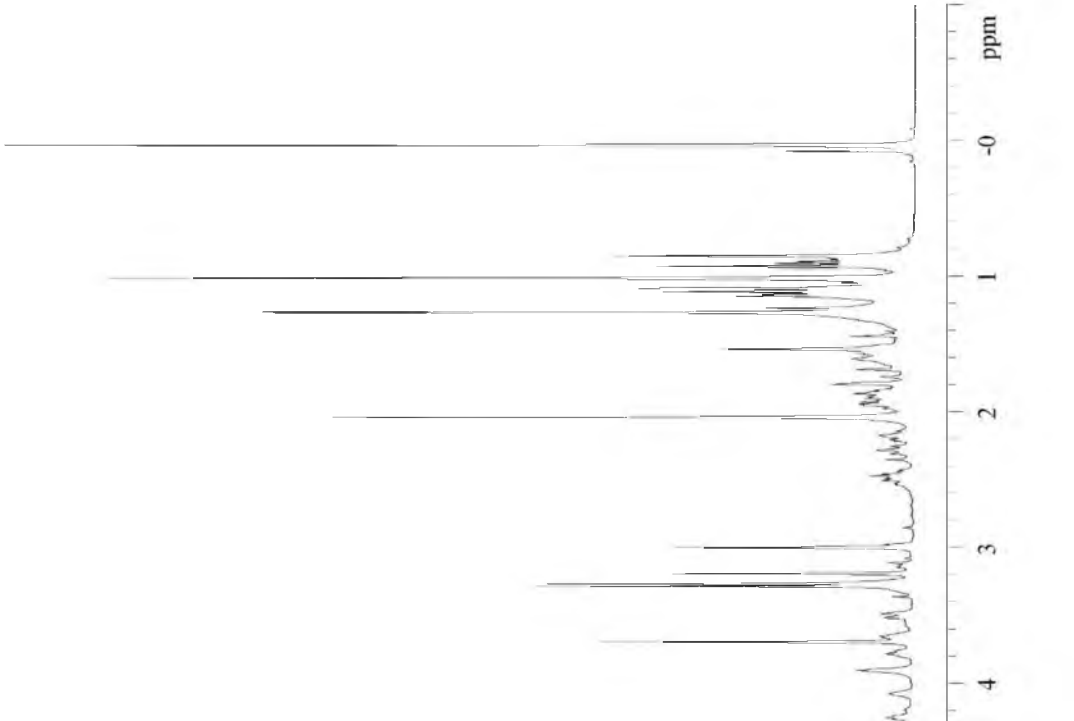


2.74
^{1}H NMR (500 MHz, $CDCl_3$)

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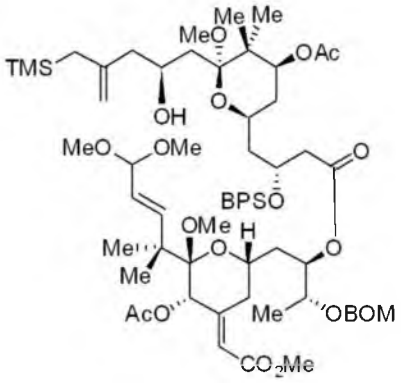
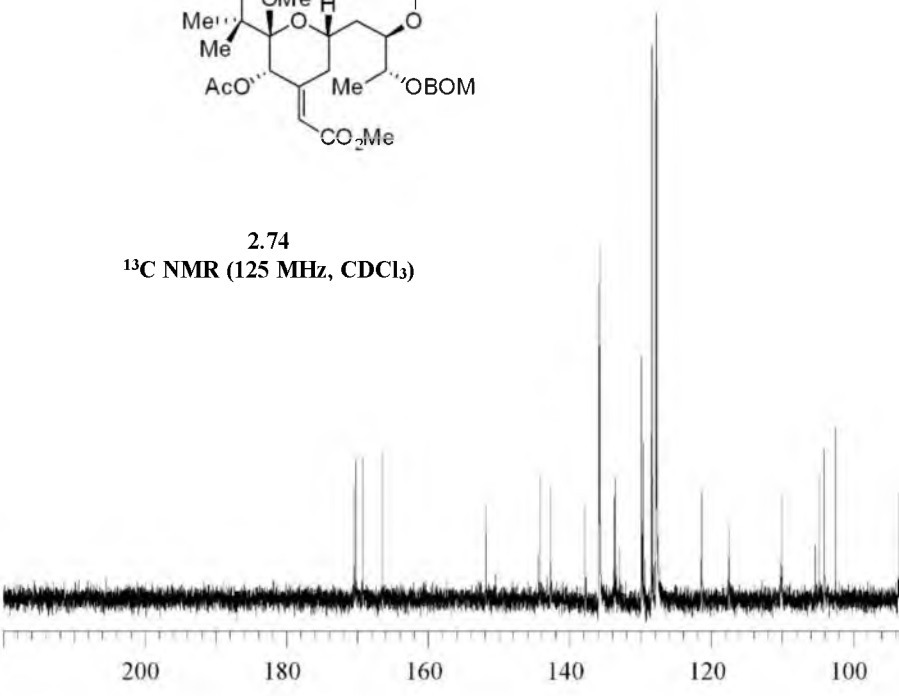
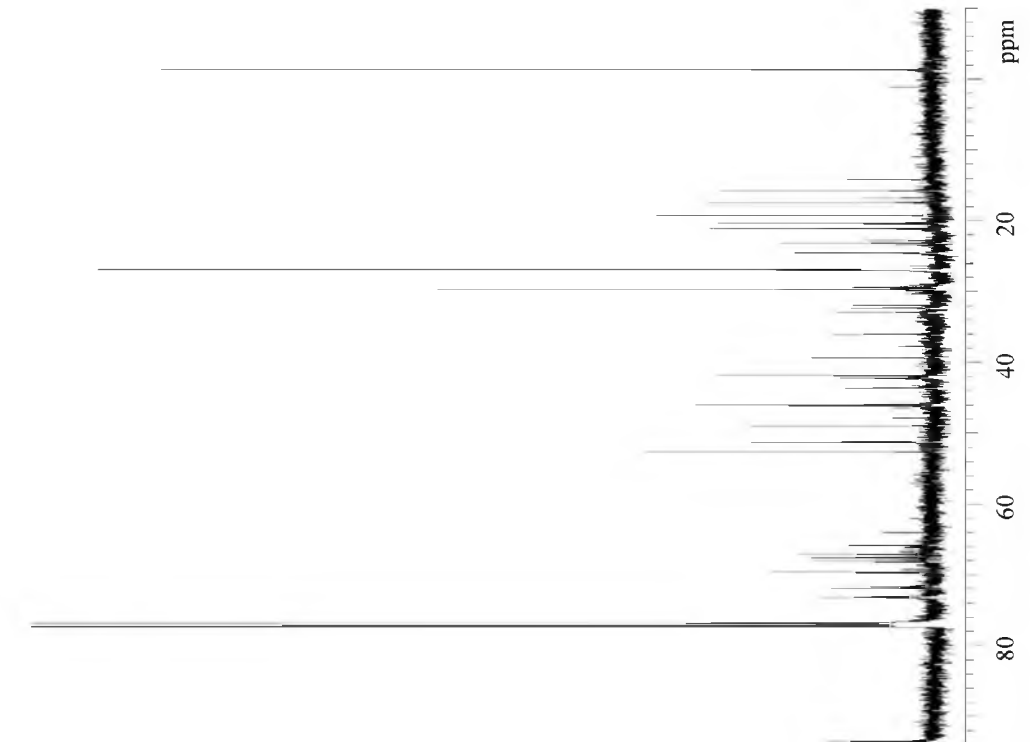


2.74

^{13}C NMR (125 MHz, $CDCl_3$)

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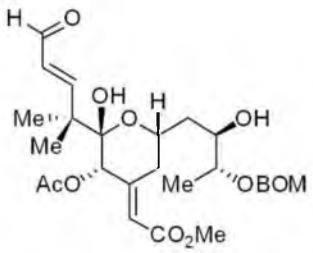
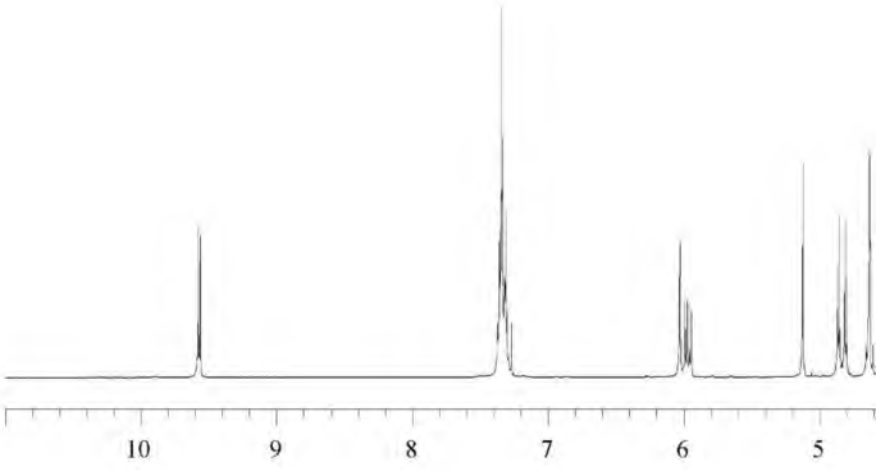
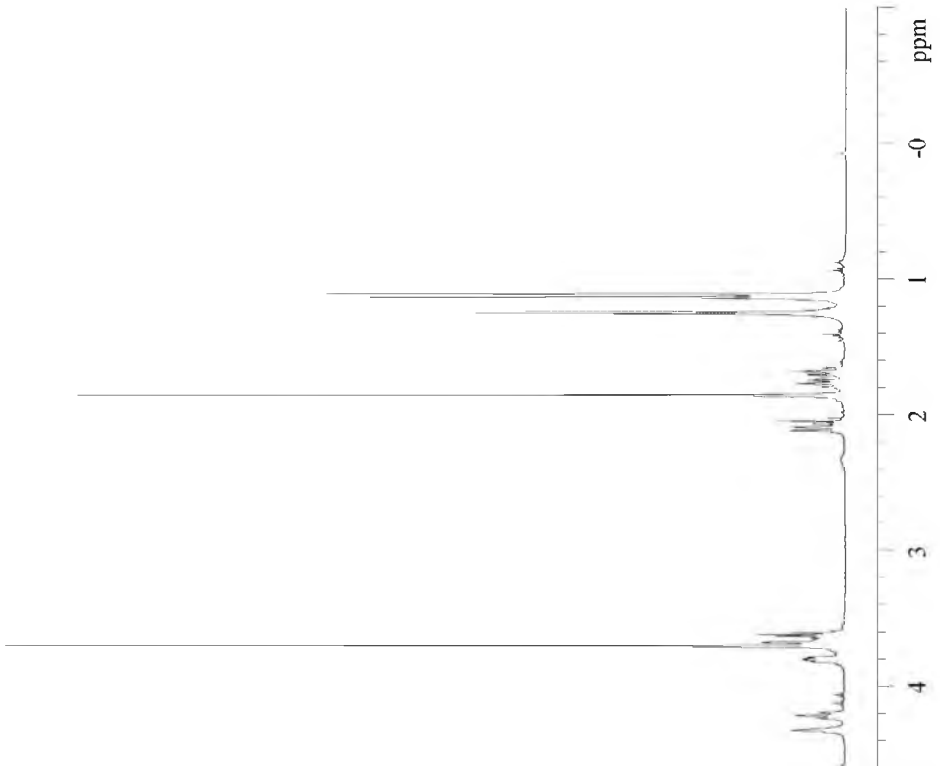


2.77
^{1}H NMR (500 MHz, $CDCl_3$)

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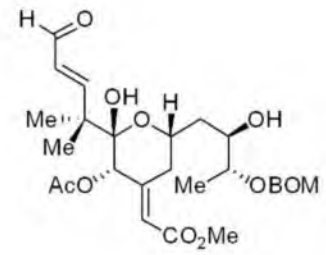
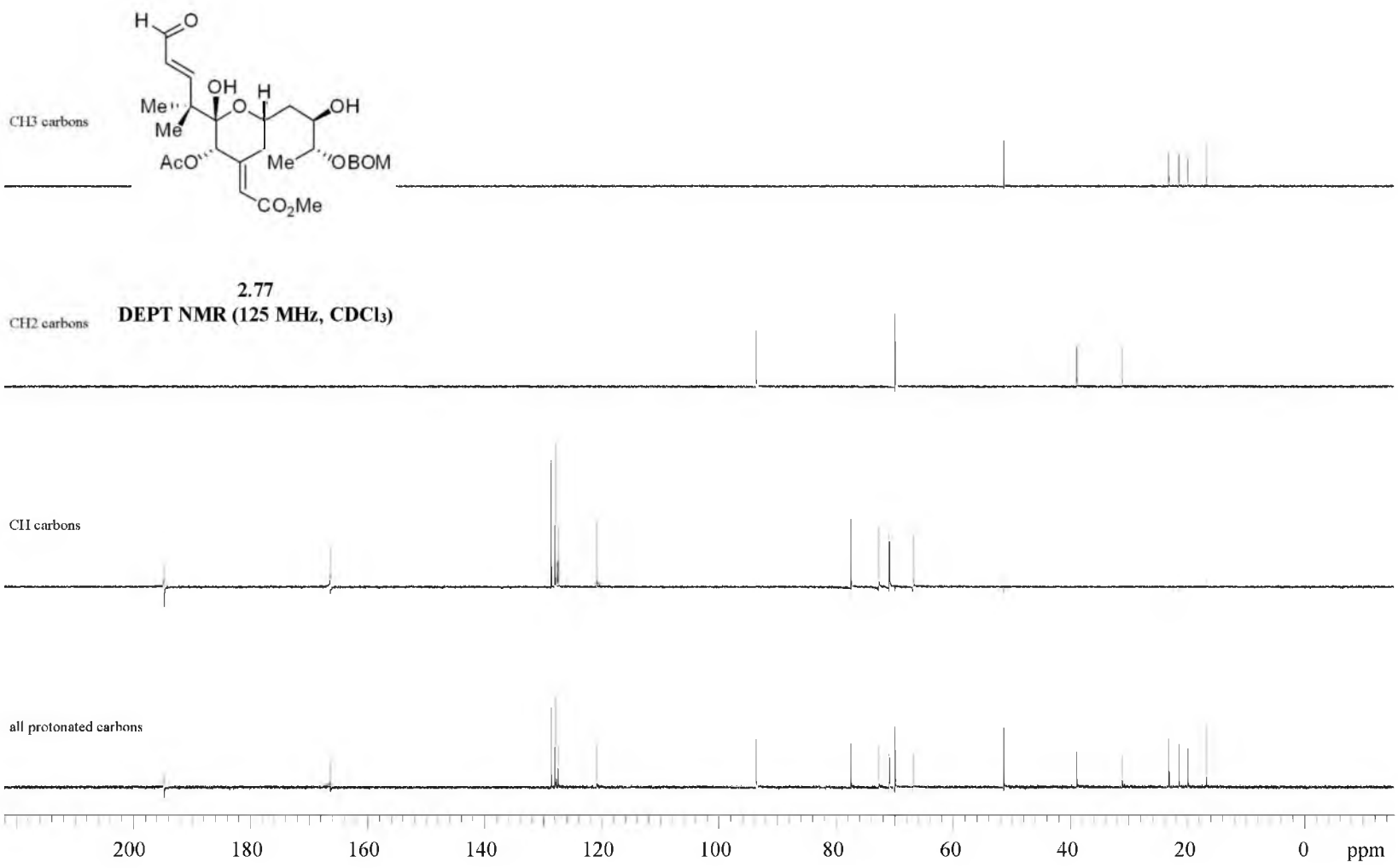
4

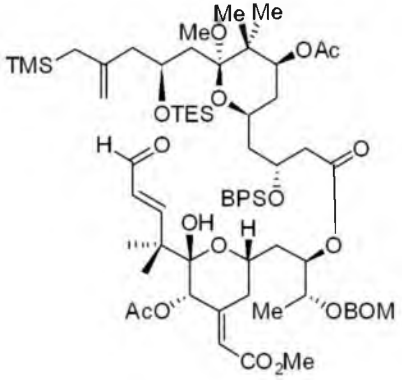


2.77
^{13}C NMR (125 MHz, $CDCl_3$)

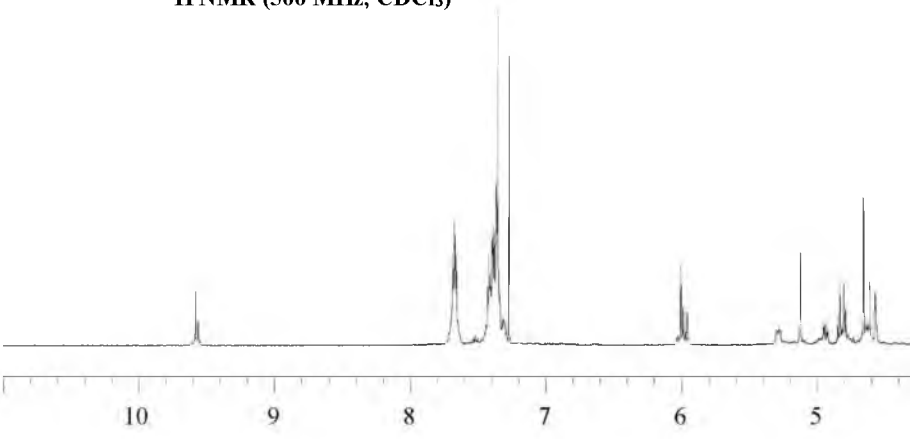


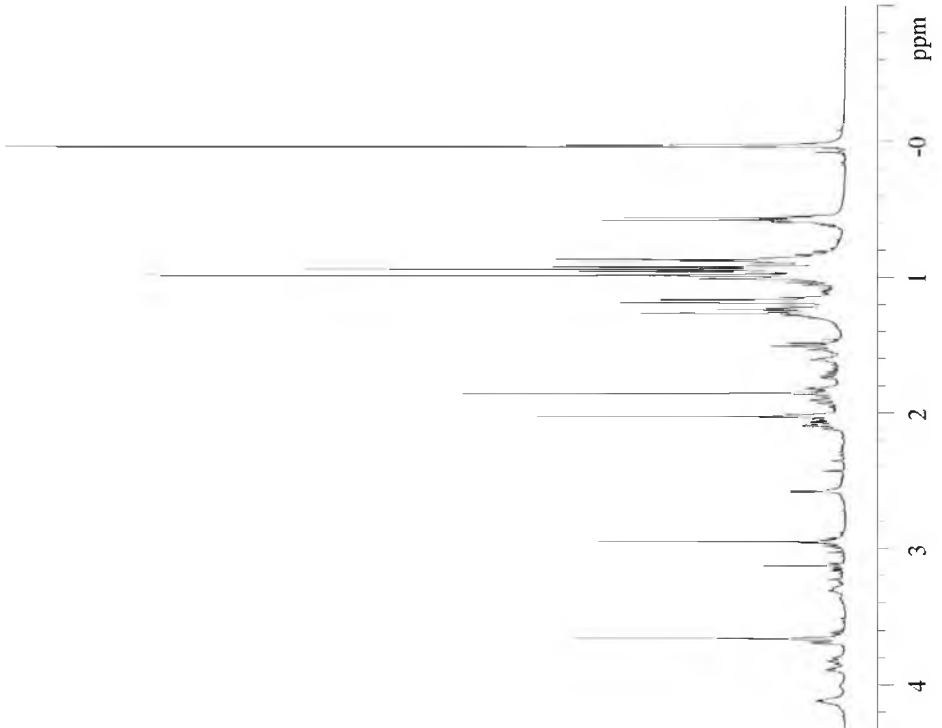
2.77

DEPT NMR (125 MHz, $CDCl_3$)



2.78
^{1}H NMR (500 MHz, $CDCl_3$)

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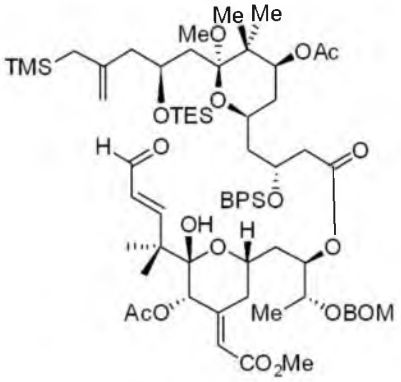
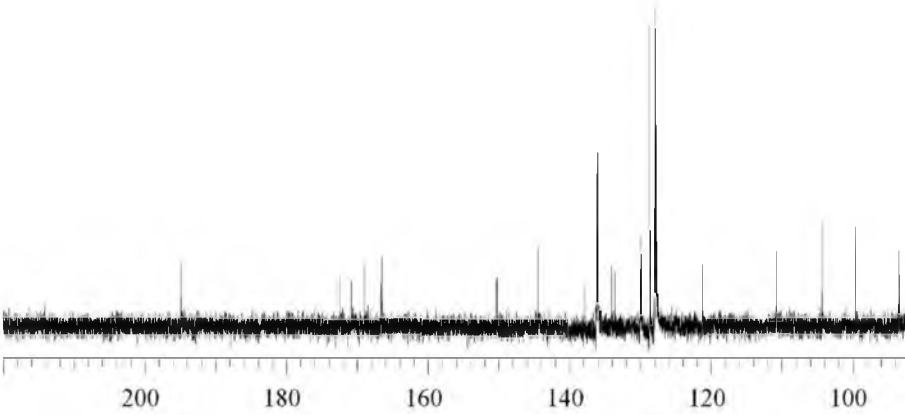


2.78
^{13}C NMR (125 MHz, $CDCl_3$)

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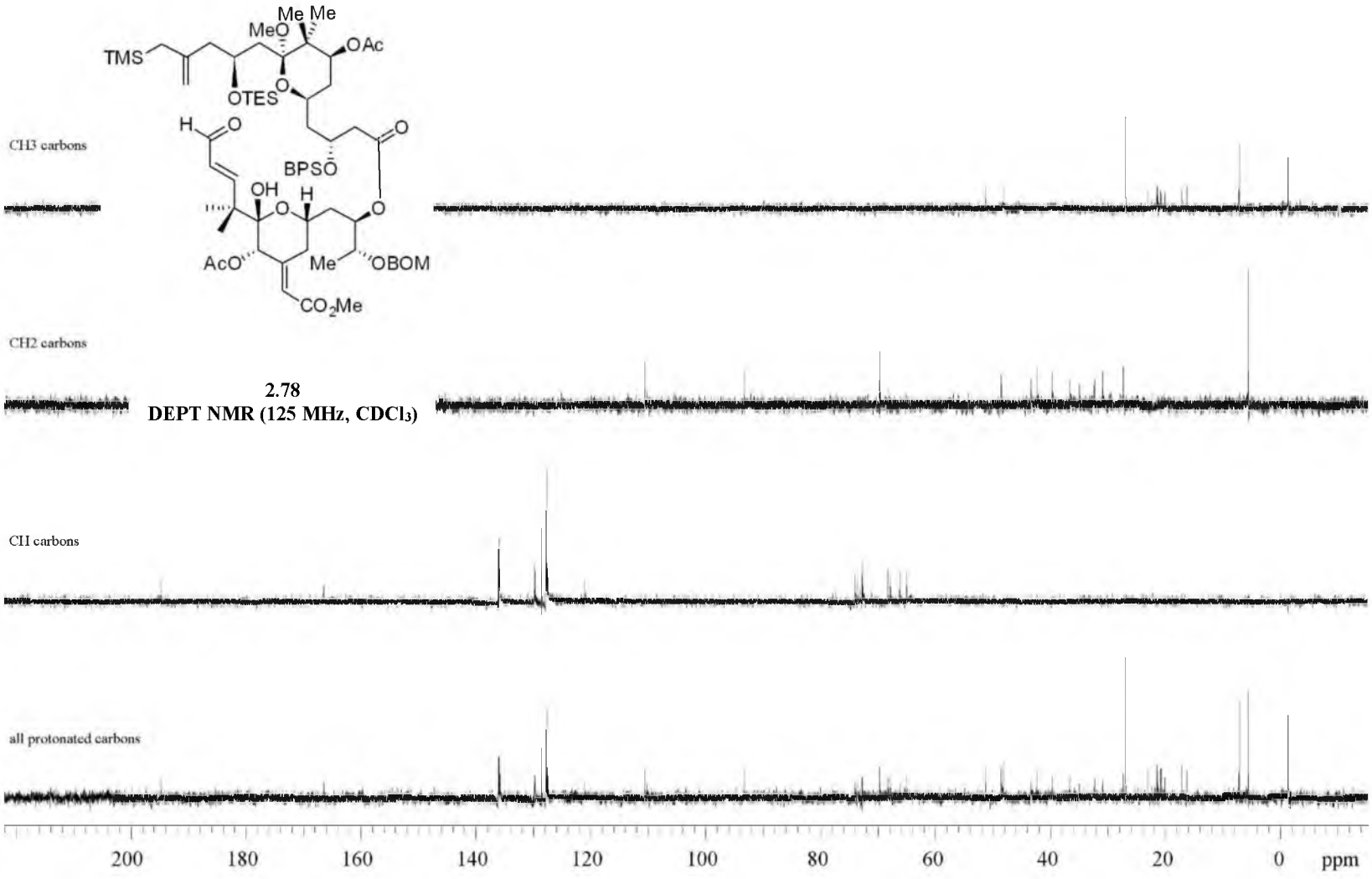
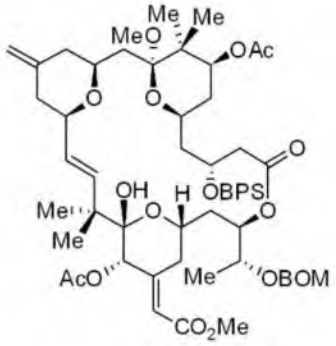
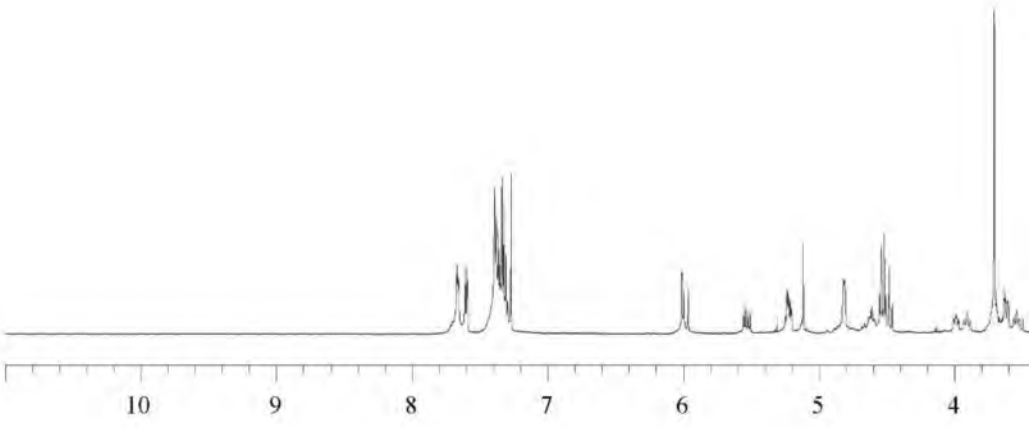
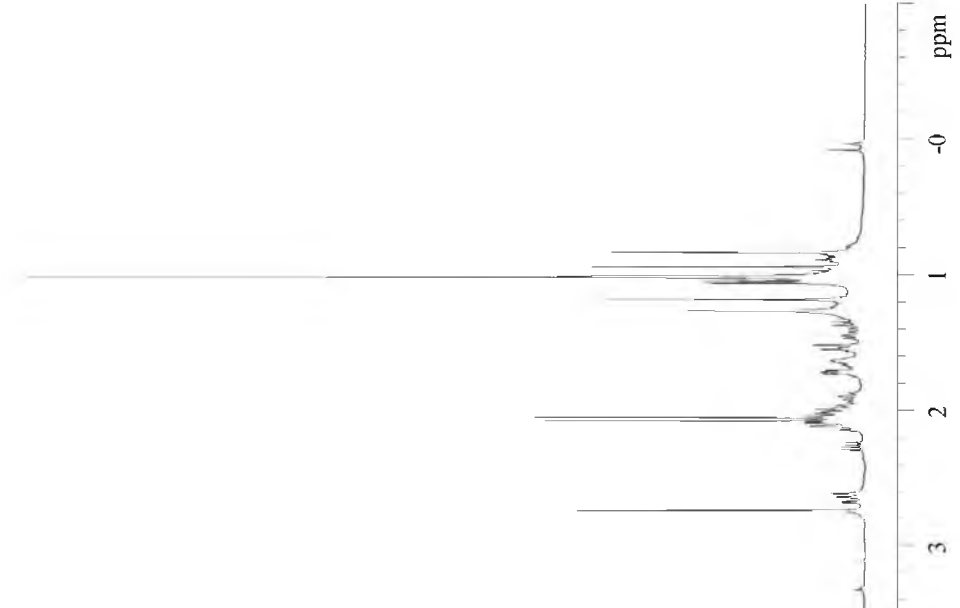


2.78
DEPT NMR (125 MHz, $CDCl_3$)



2.79
^{1}H NMR (500 MHz, $CDCl_3$)

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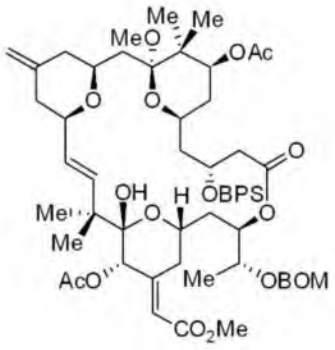
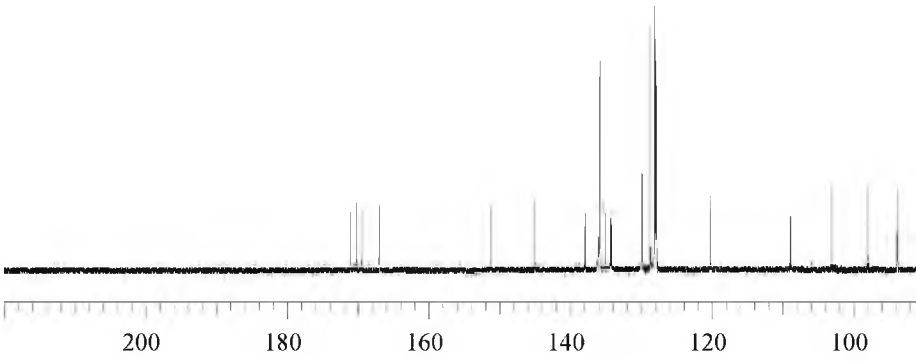


2.79
^{13}C NMR (125 MHz, $CDCl_3$)

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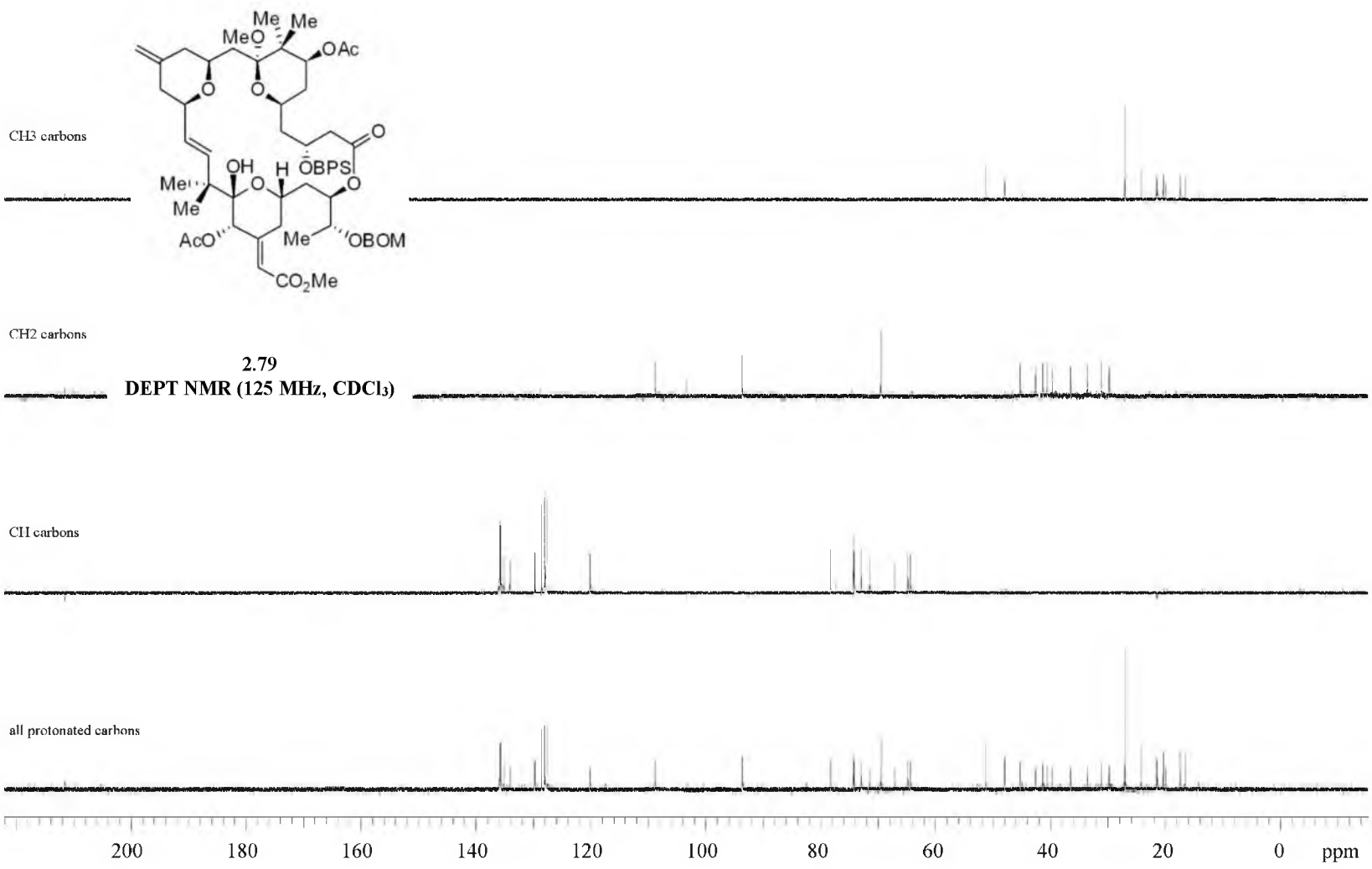
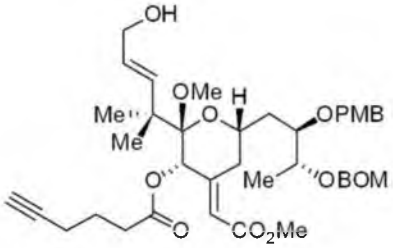
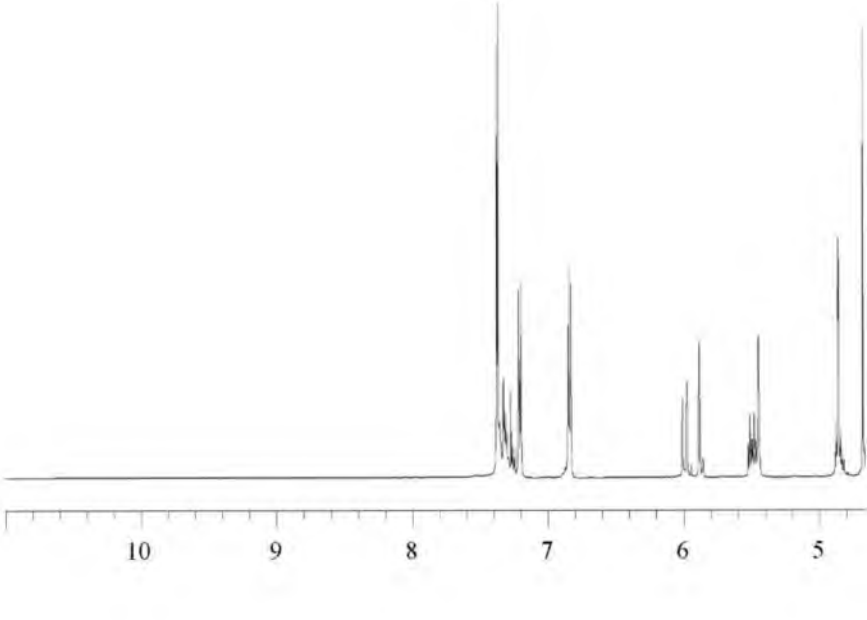
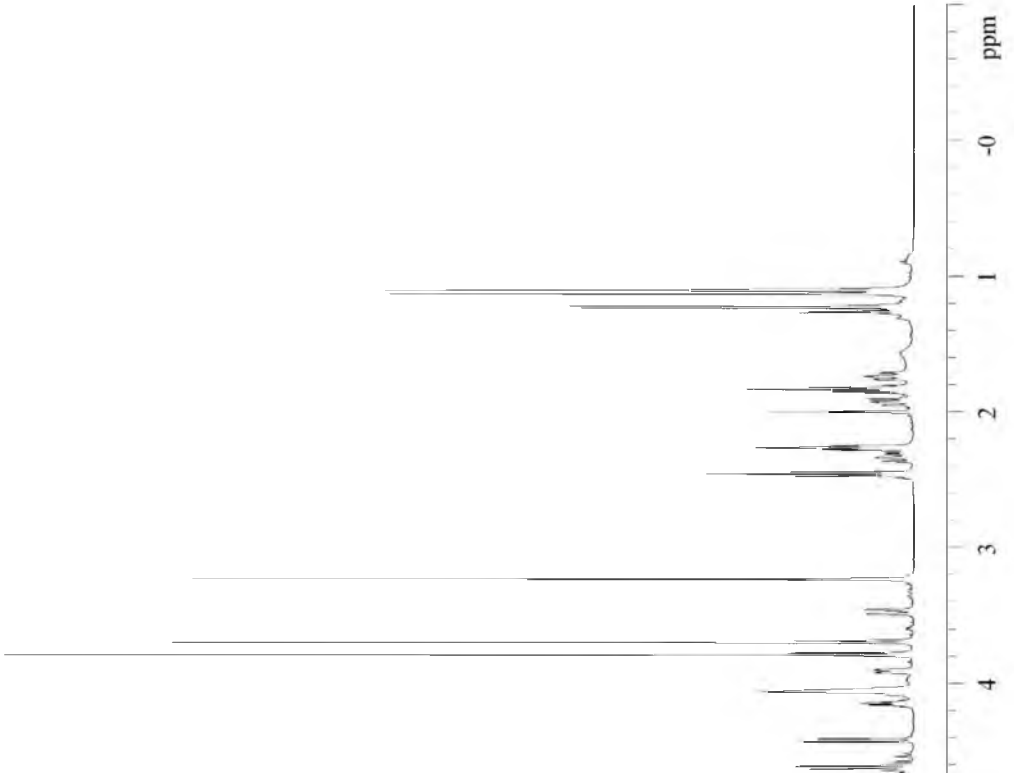


2.79
DEPT NMR (125 MHz, $CDCl_3$)



2.81
^{1}H NMR (500 MHz, $CDCl_3$)

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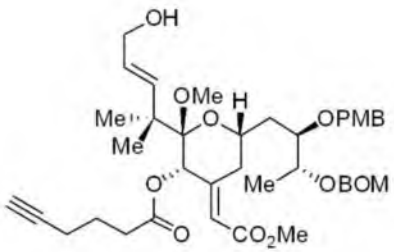
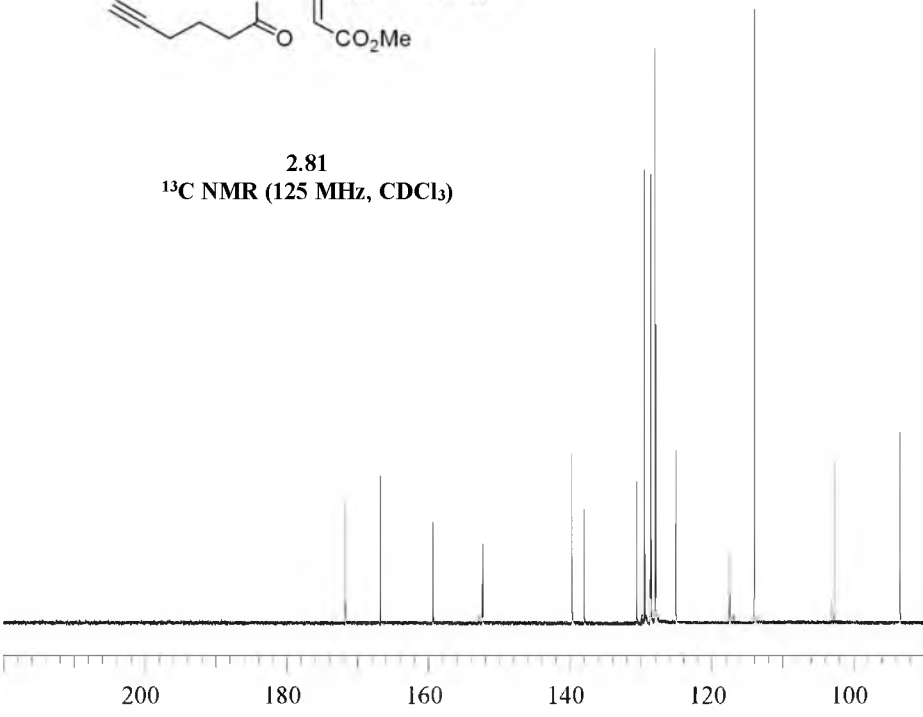
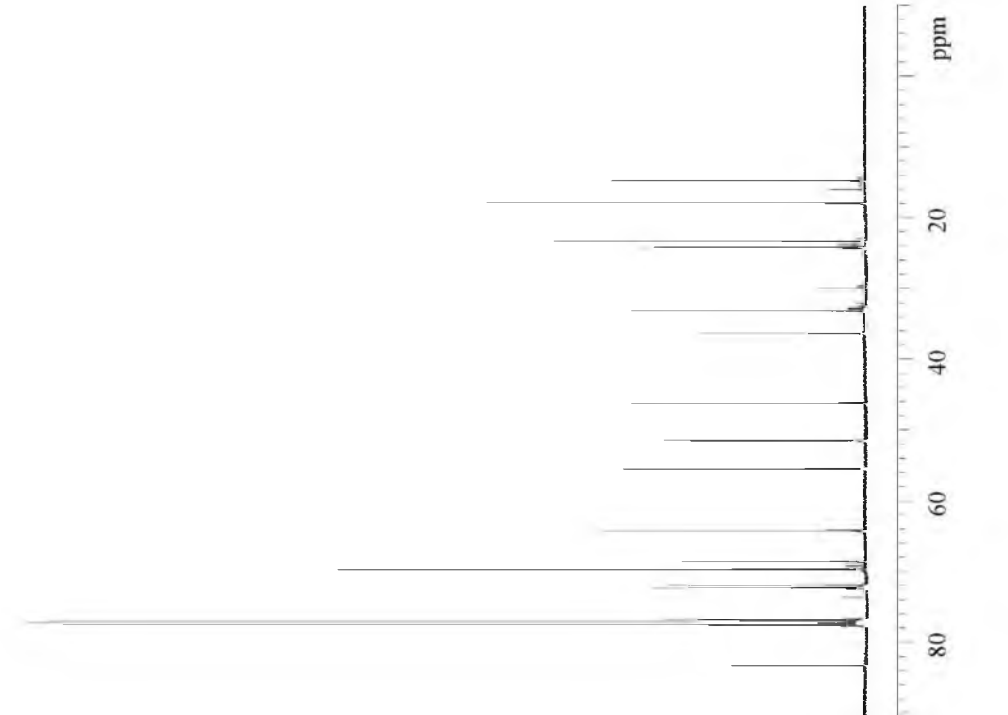


2.81
^{13}C NMR (125 MHz, $CDCl_3$)

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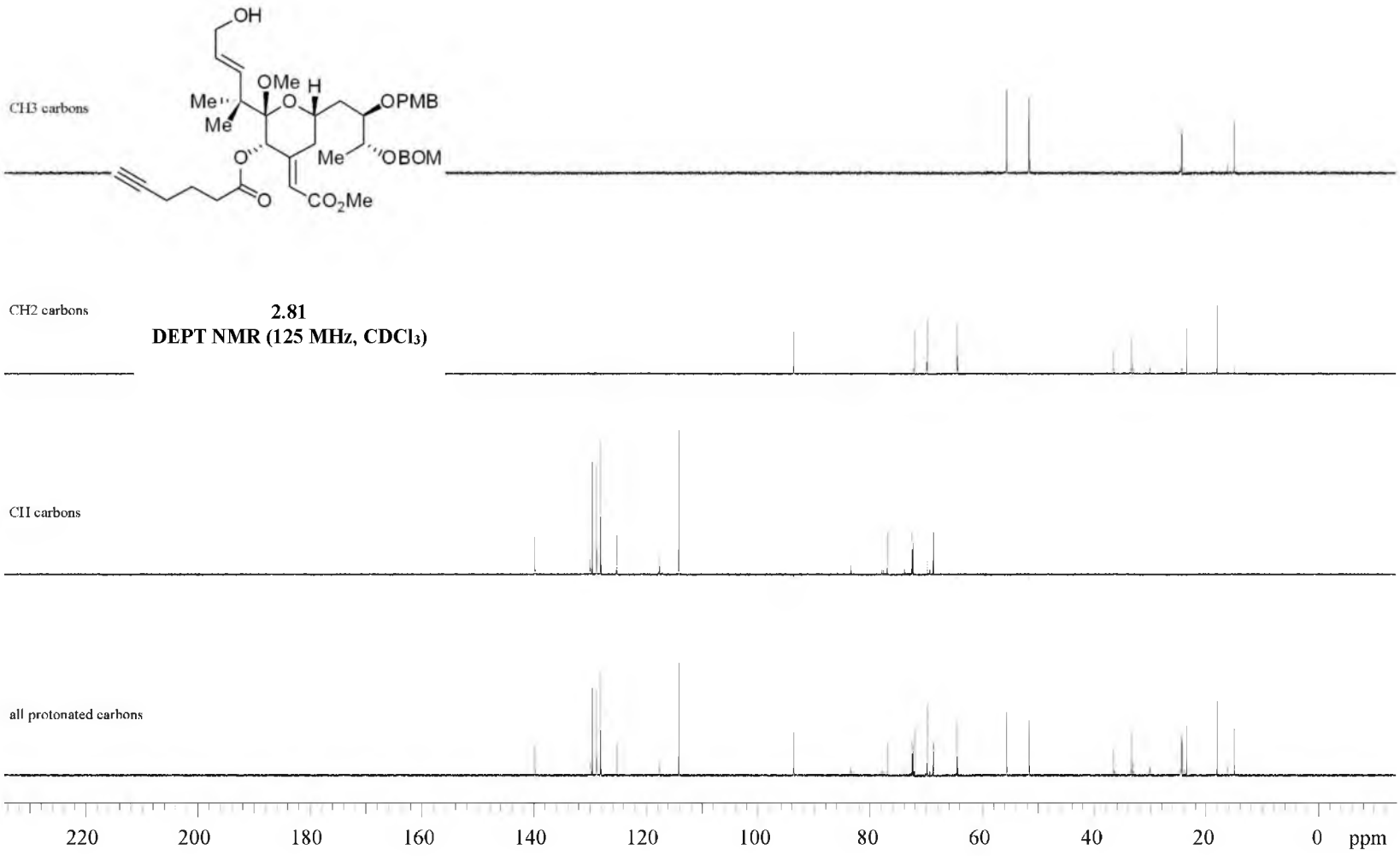
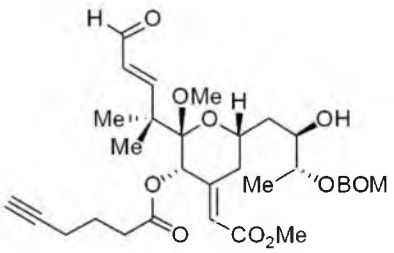
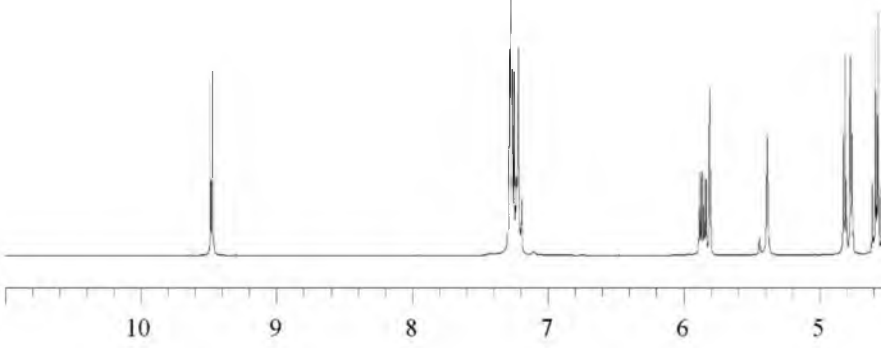


2.81
DEPT NMR (125 MHz, $CDCl_3$)



2.82
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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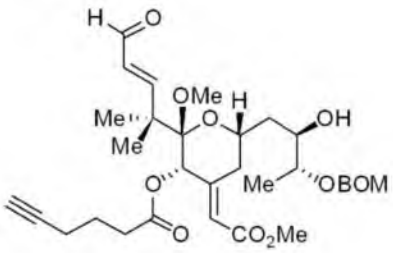
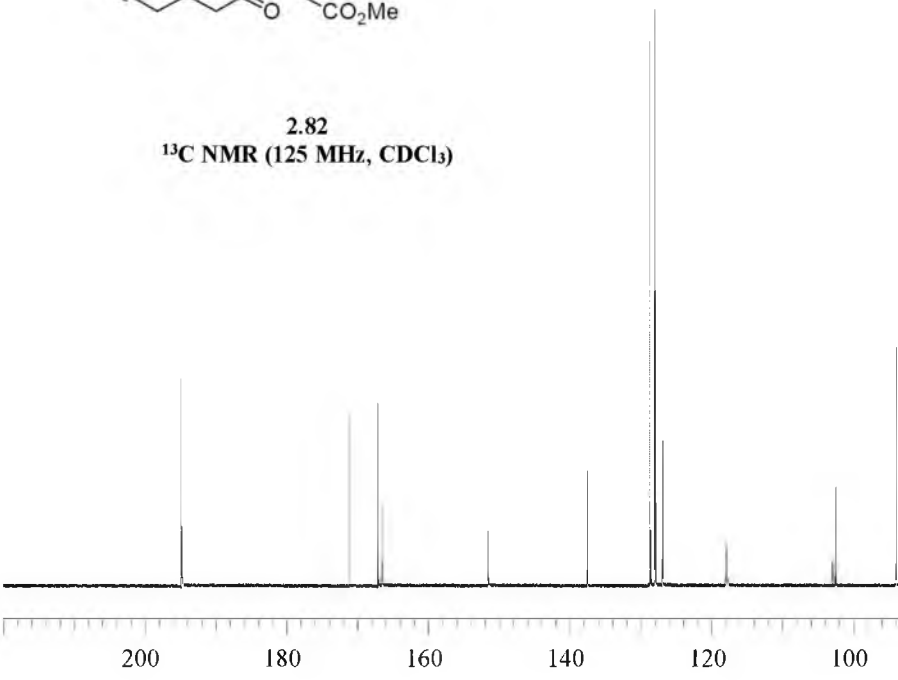
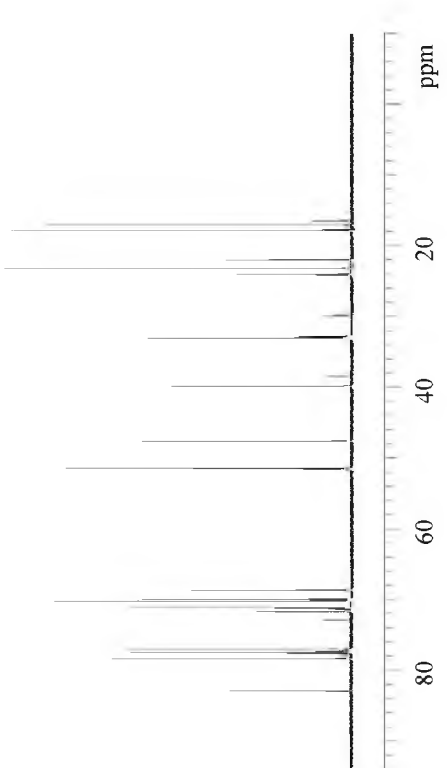


2.82
^{13}C NMR (125 MHz, $CDCl_3$)

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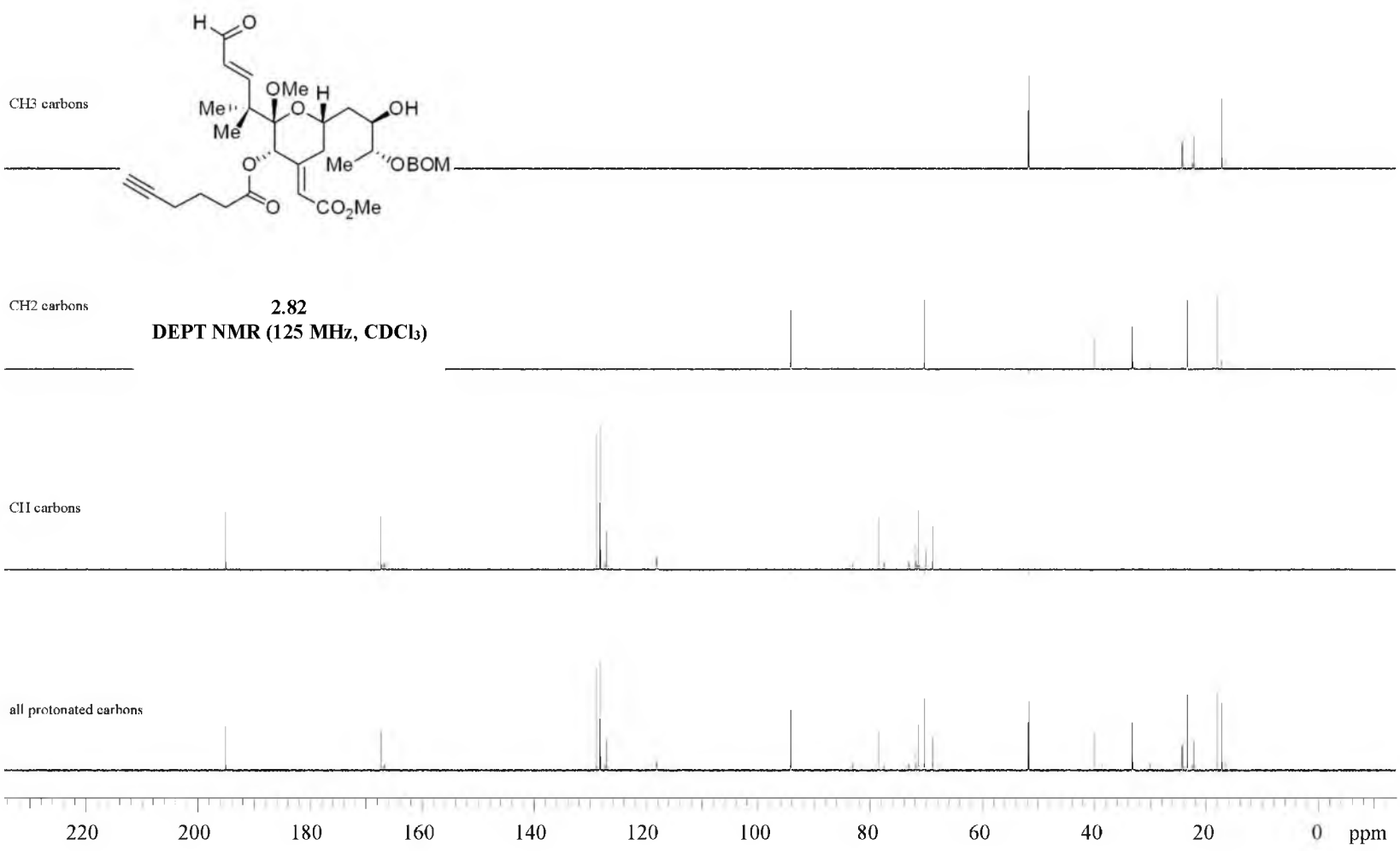
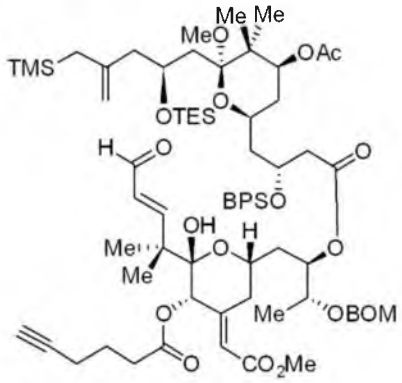
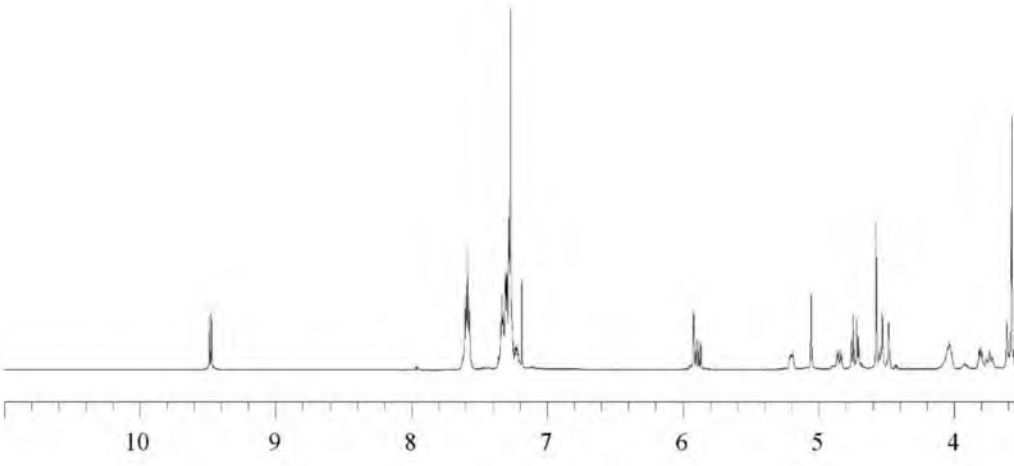


2.82
DEPT NMR (125 MHz, $CDCl_3$)



2.83

^{1}H NMR (500 MHz, $CDCl_3$)

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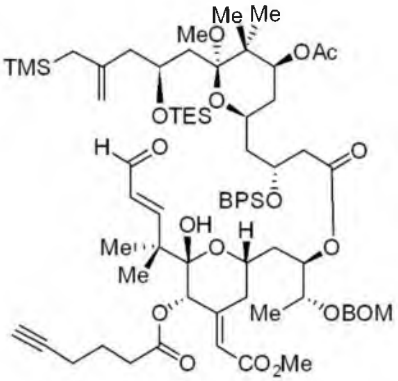
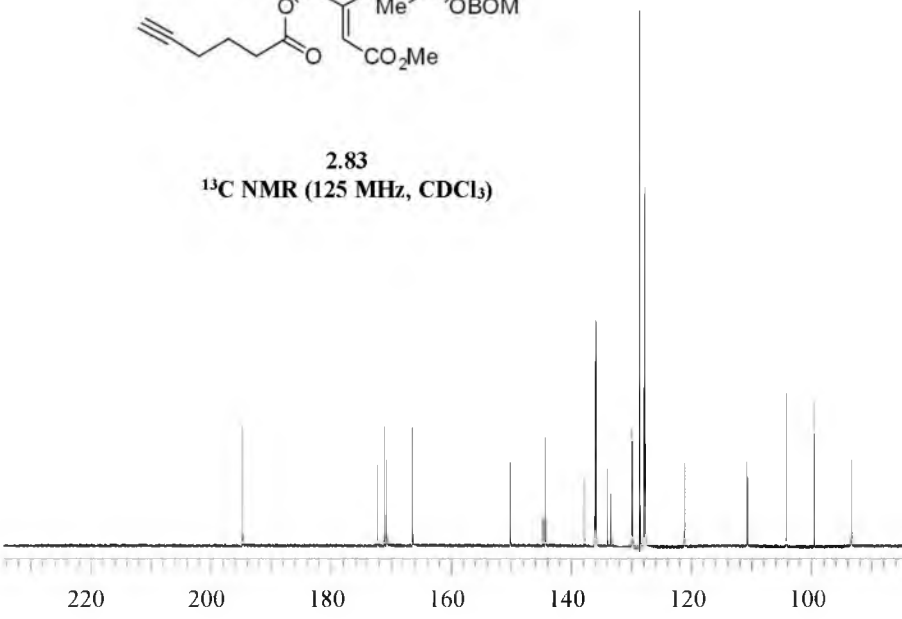
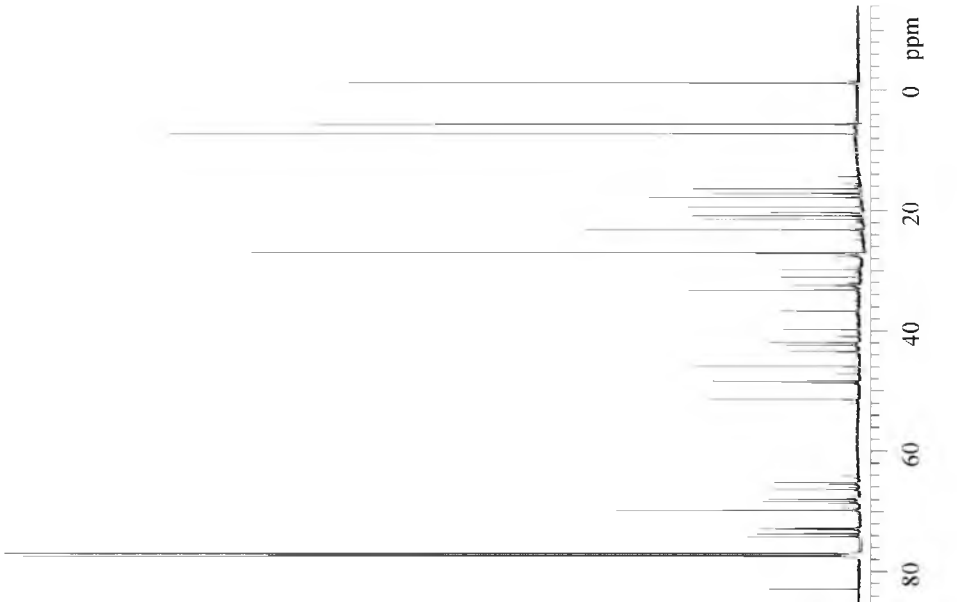


2.83
^{13}C NMR (125 MHz, $CDCl_3$)

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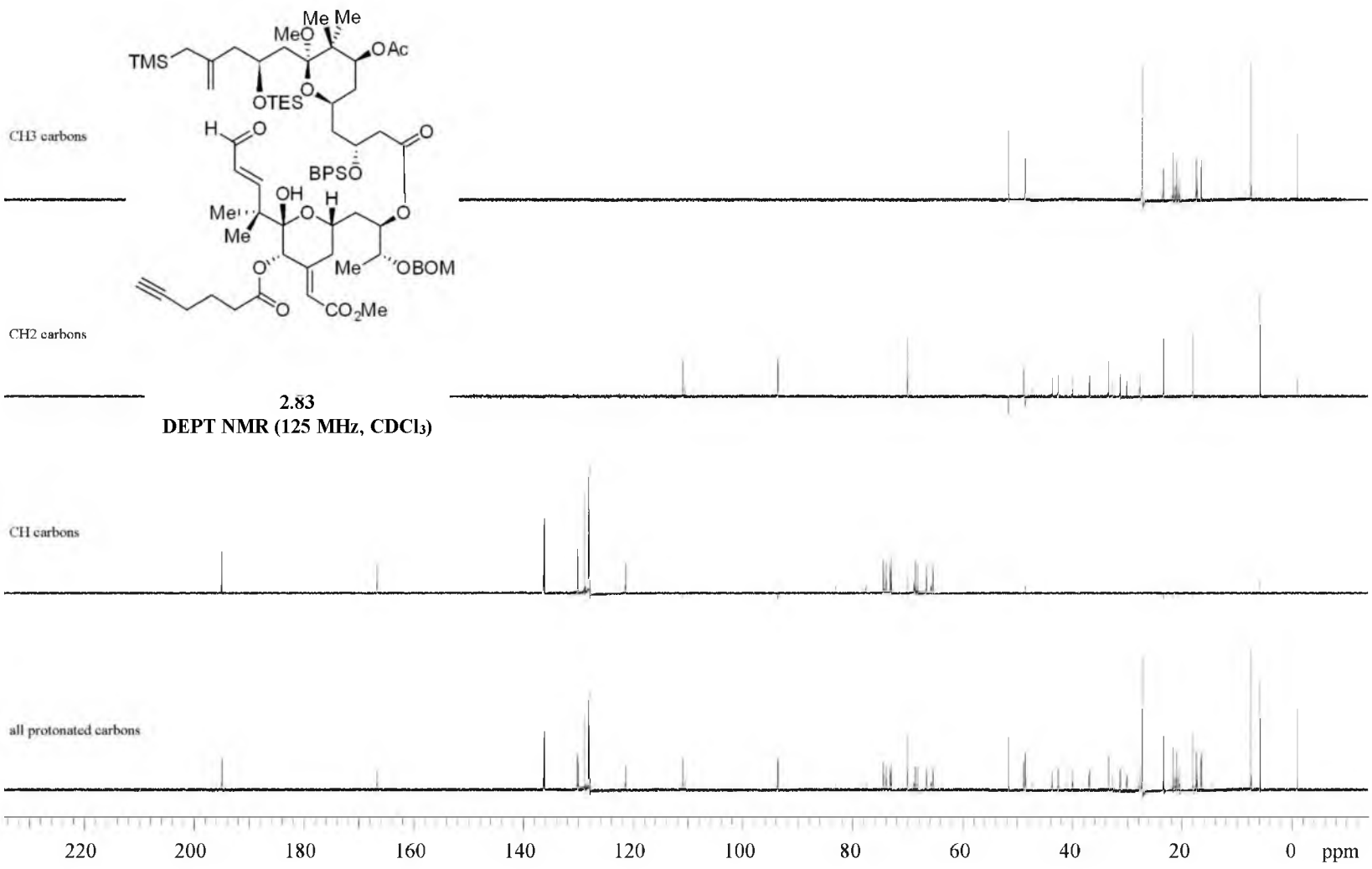
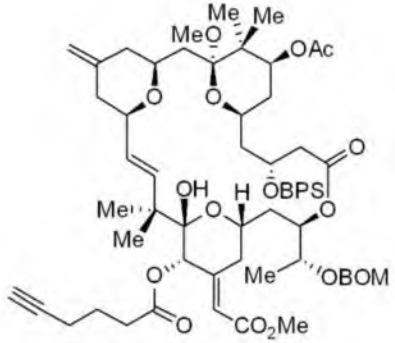
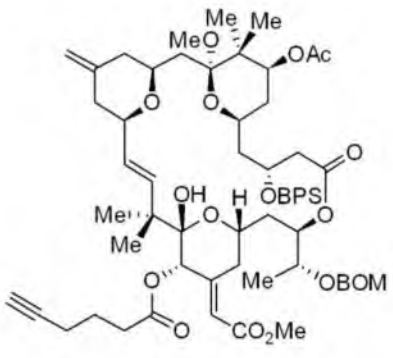


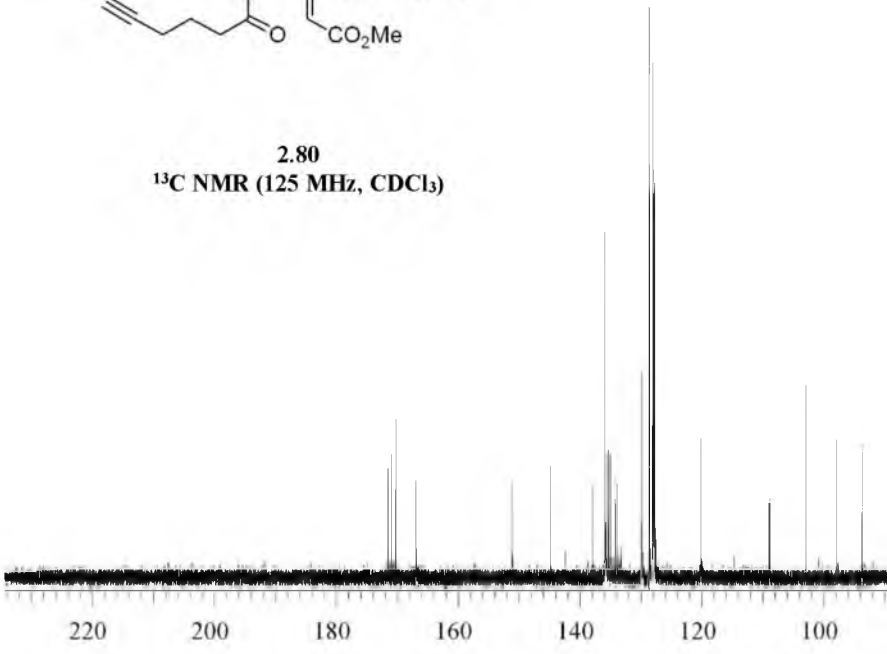
2.83
DEPT NMR (125 MHz, $CDCl_3$)



2.80
^{1}H NMR (500 MHz, $CDCl_3$)



2.80
^{13}C NMR (125 MHz, $CDCl_3$)

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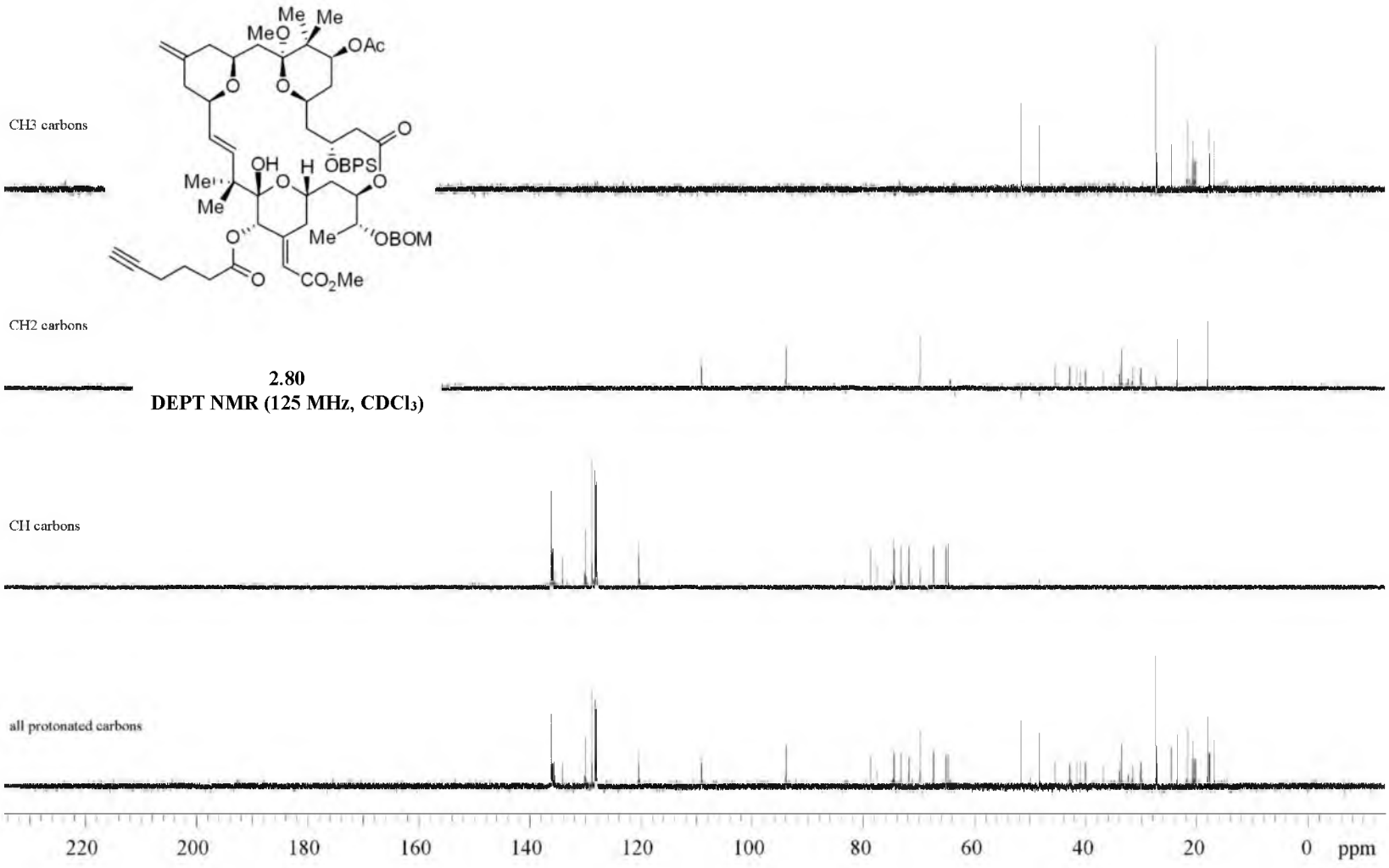
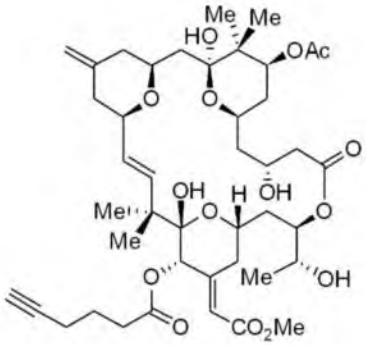
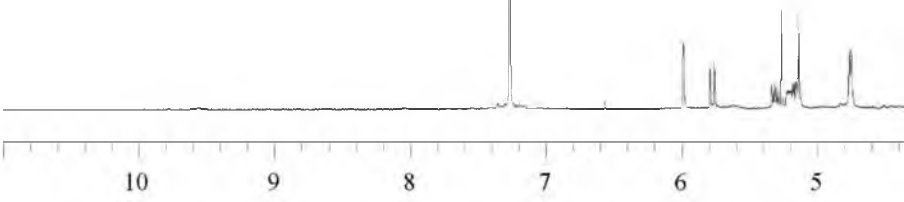
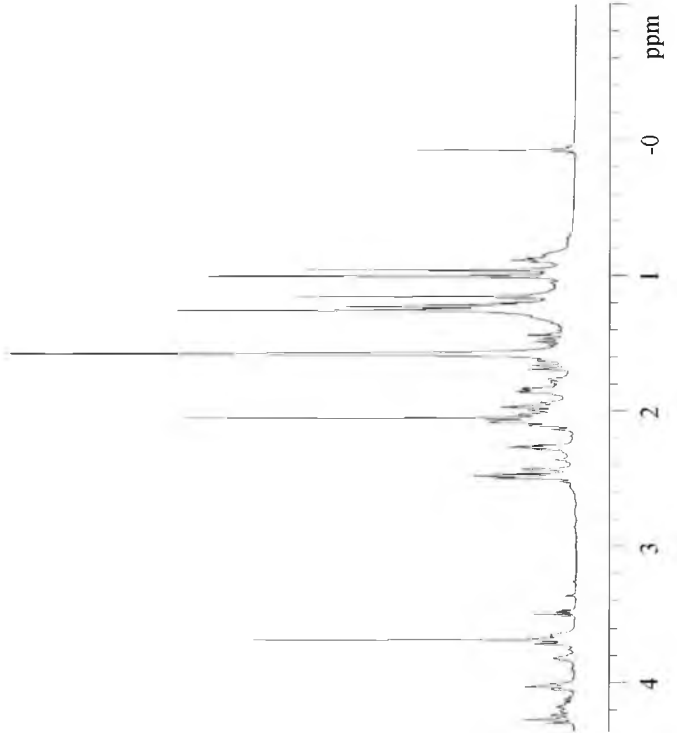


2.80
DEPT NMR (125 MHz, $CDCl_3$)



2.84
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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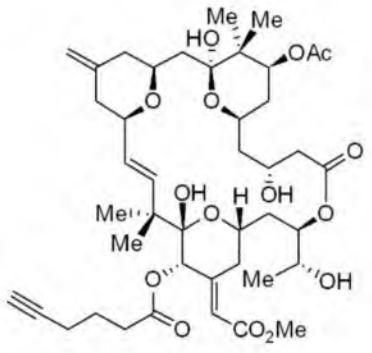
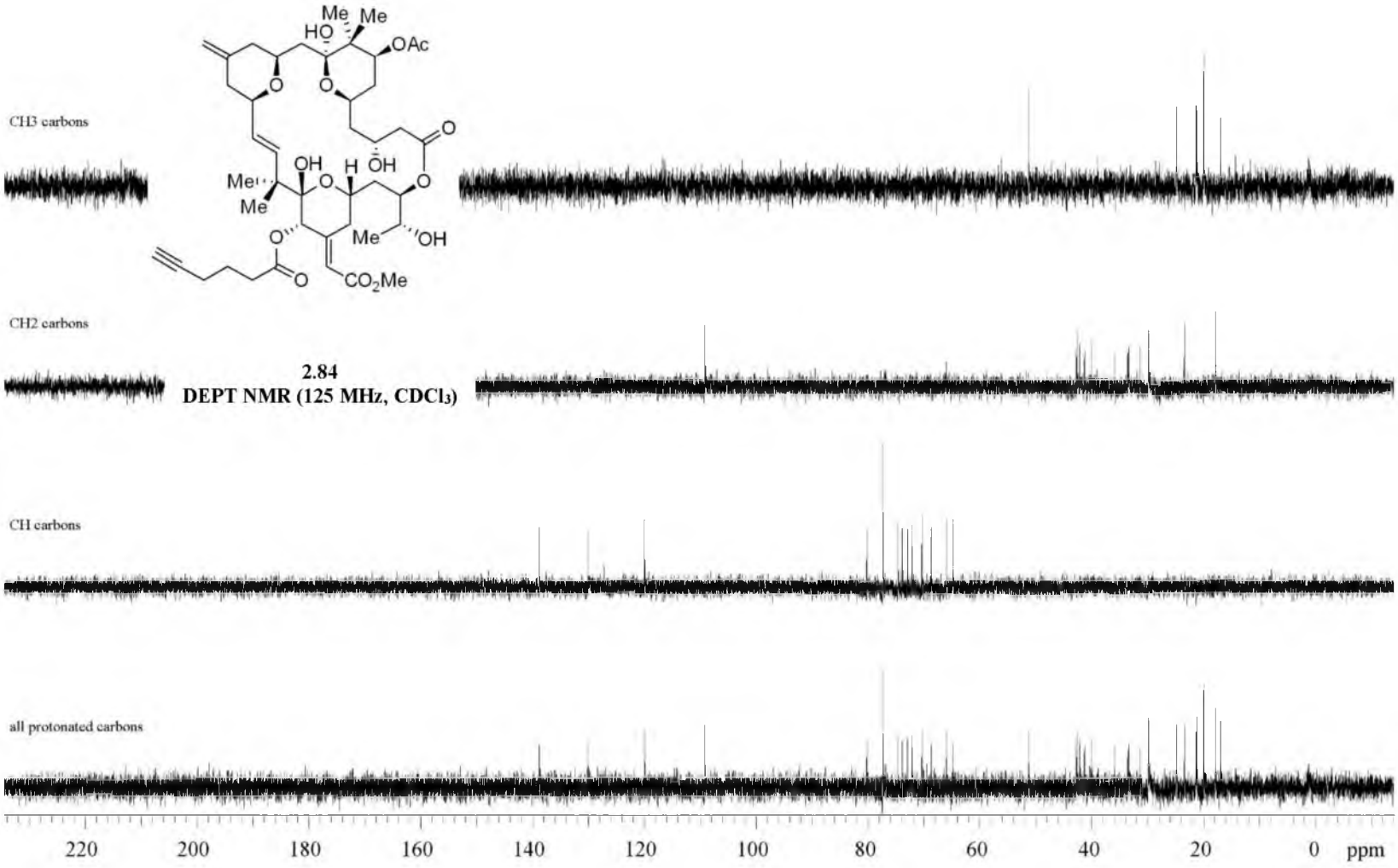
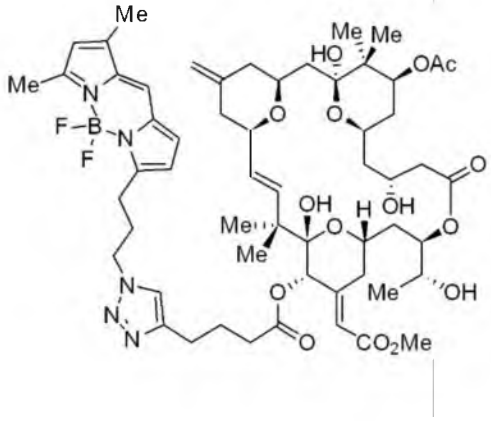


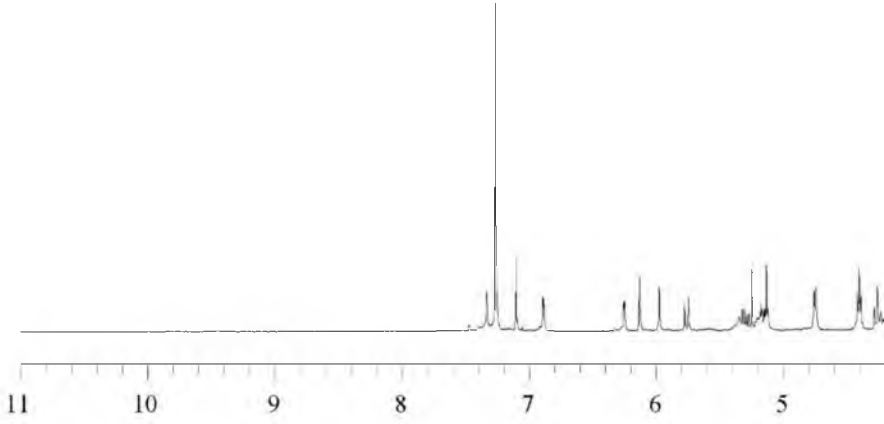
2.84
^{13}C NMR (125 MHz, $CDCl_3$)

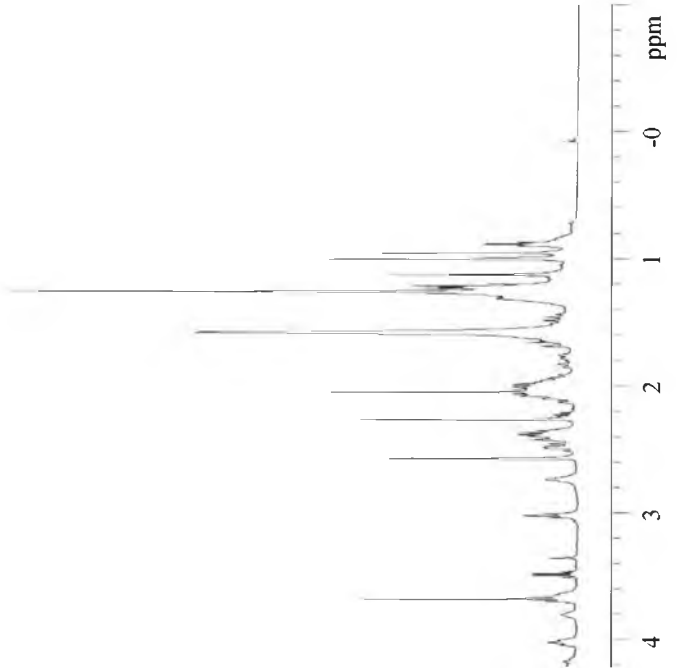


2.84
DEPT NMR (125 MHz, $CDCl_3$)



Merle 45
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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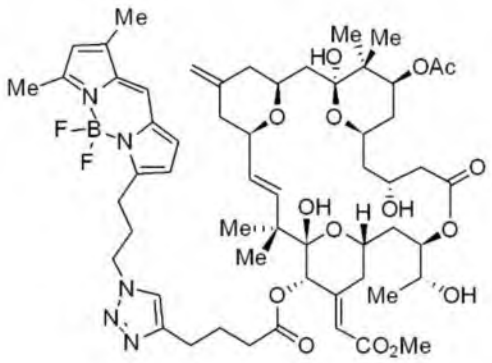
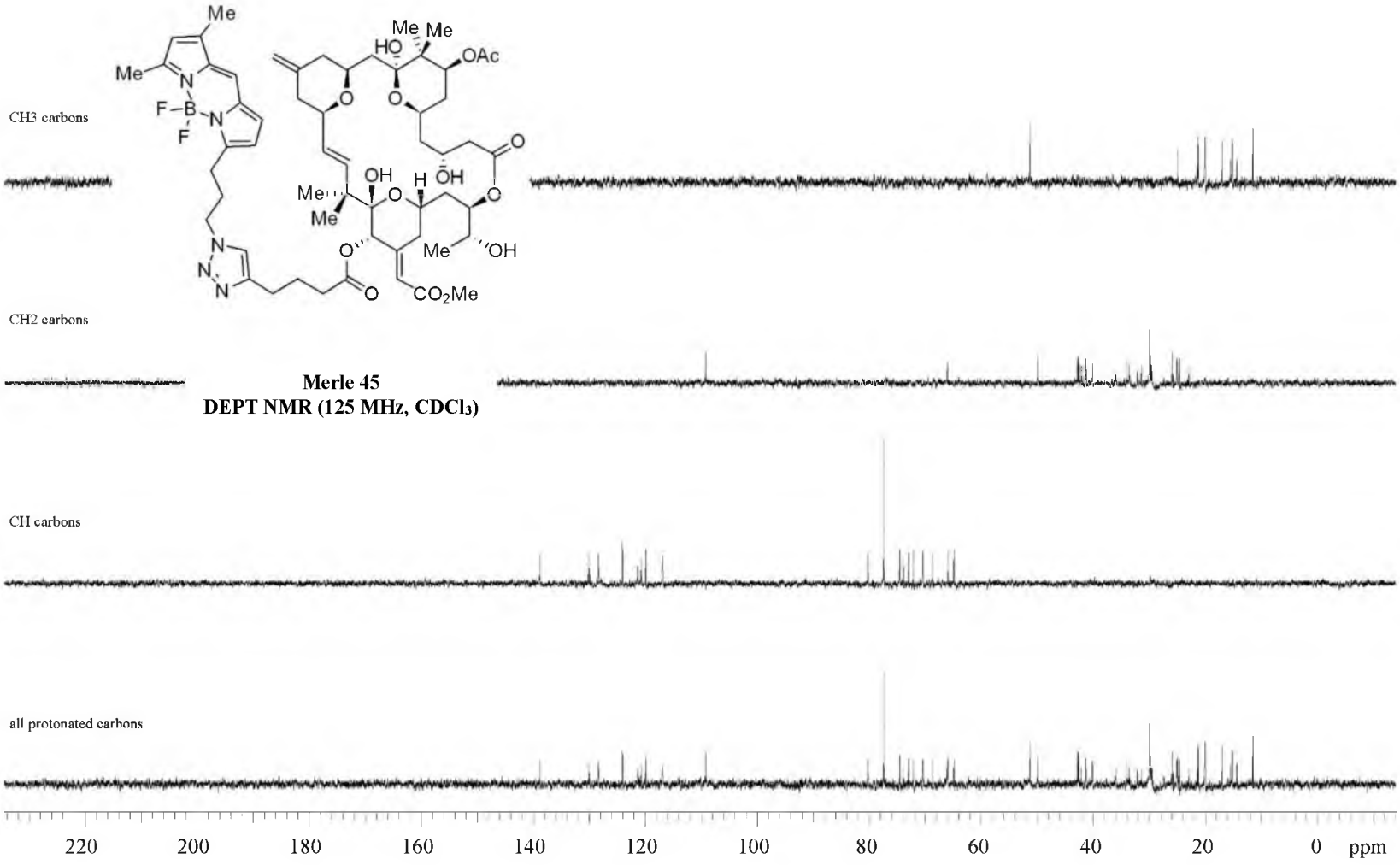


Merle 45
^{13}C NMR (125 MHz, $CDCl_3$)

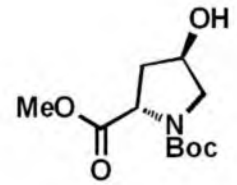


Merle 45
DEPT NMR (125 MHz, $CDCl_3$)

APPENDIX C

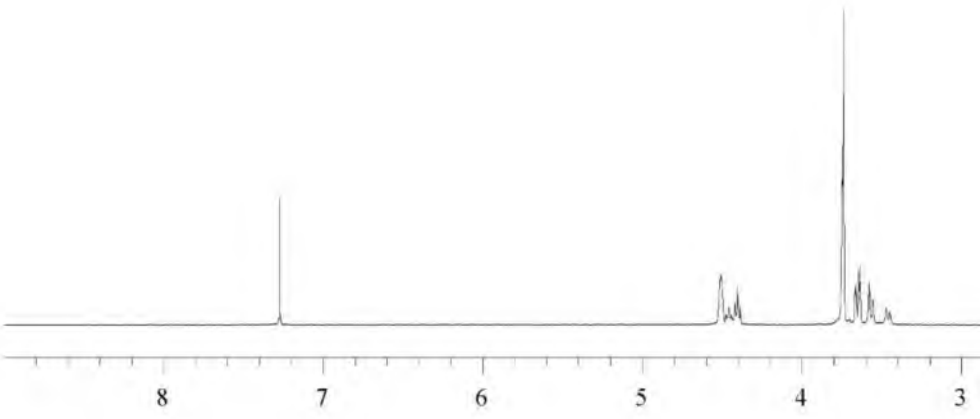
^{1}H, ^{13}C, DEPT SPECTRA AND CRYSTAL STRUCTURE REPORT

FOR CHAPTER 3



3.42

^{1}H NMR (500 MHz, $CDCl_3$)




ppm
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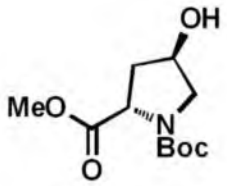
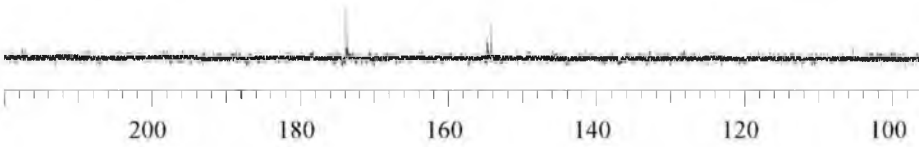


3.42
^{13}C NMR (125 MHz, $CDCl_3$)




ppm
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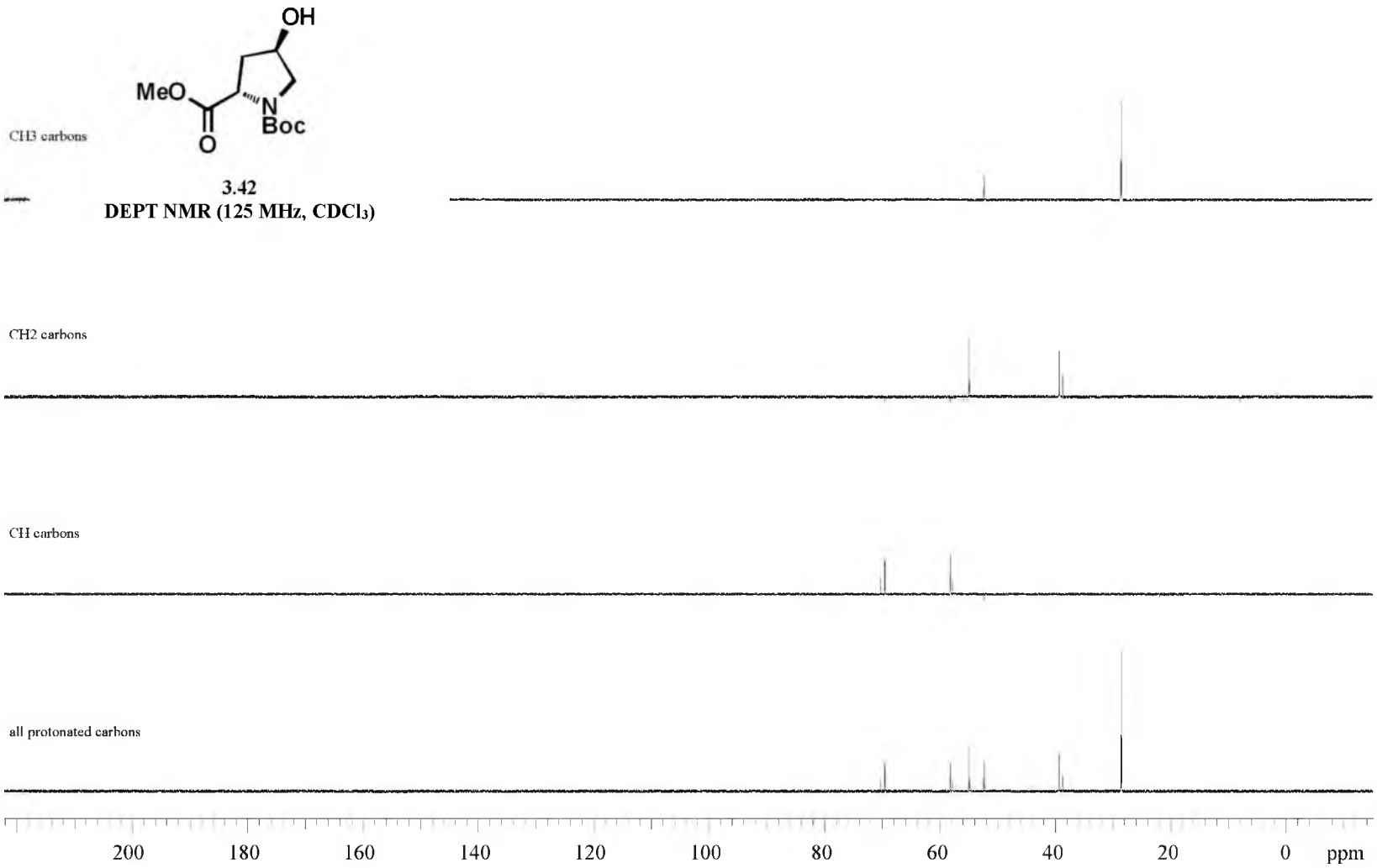
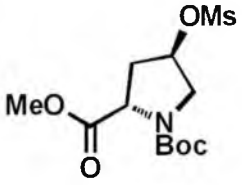
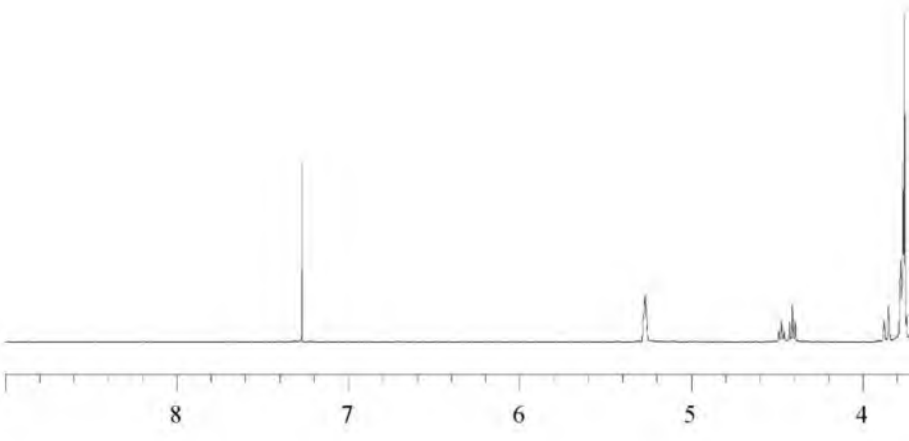


3.42
DEPT NMR (125 MHz, $CDCl_3$)



3.43
^{1}H NMR (500 MHz, $CDCl_3$)

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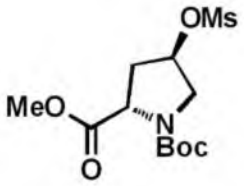
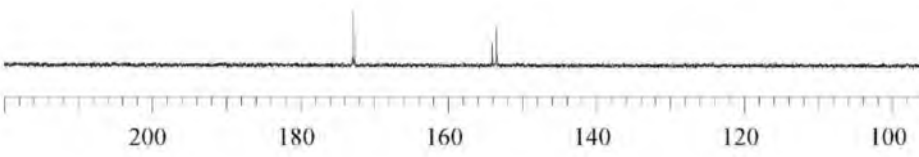
ppm



3.43
^{13}C NMR (125 MHz, $CDCl_3$)

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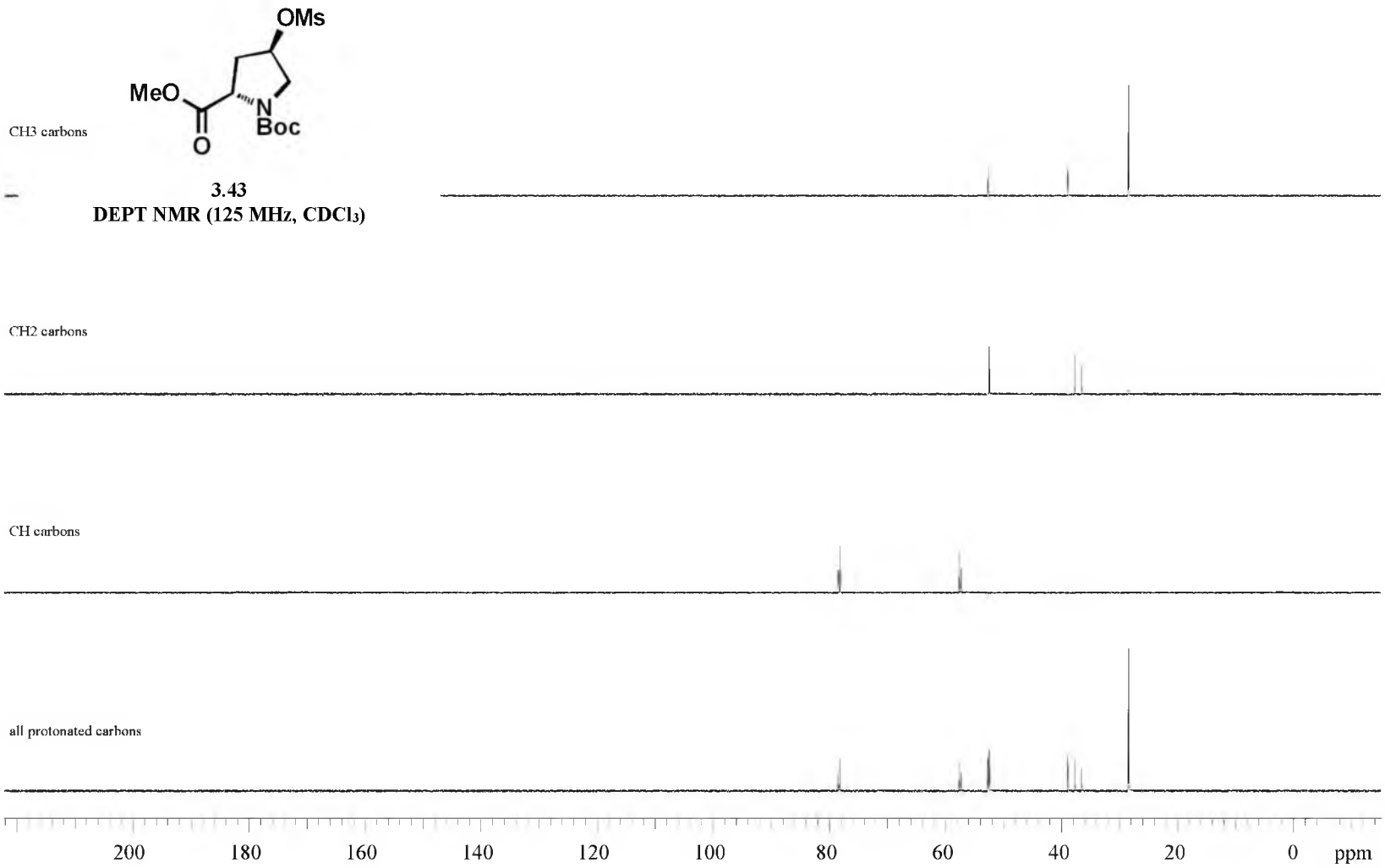
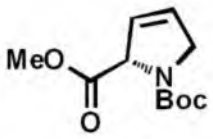
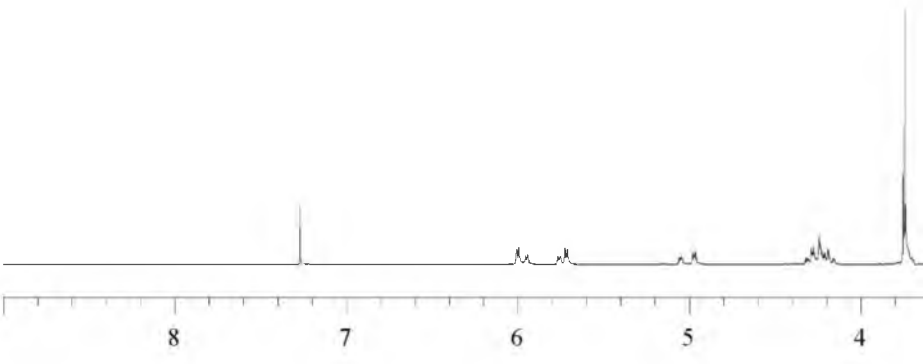
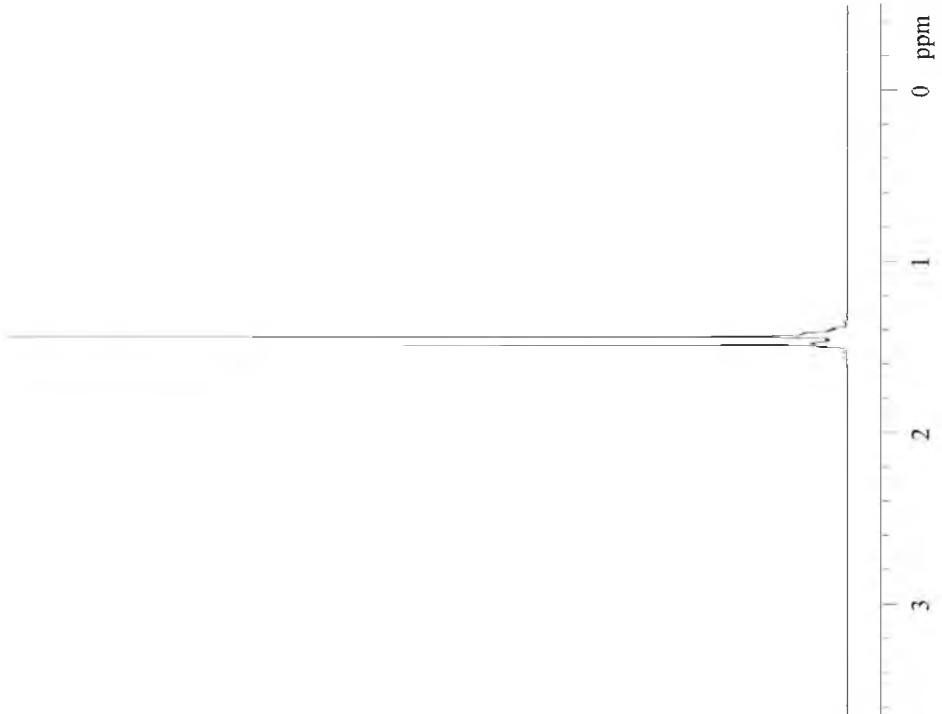


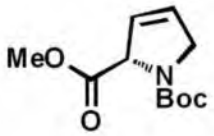
3.43
DEPT NMR (125 MHz, $CDCl_3$)



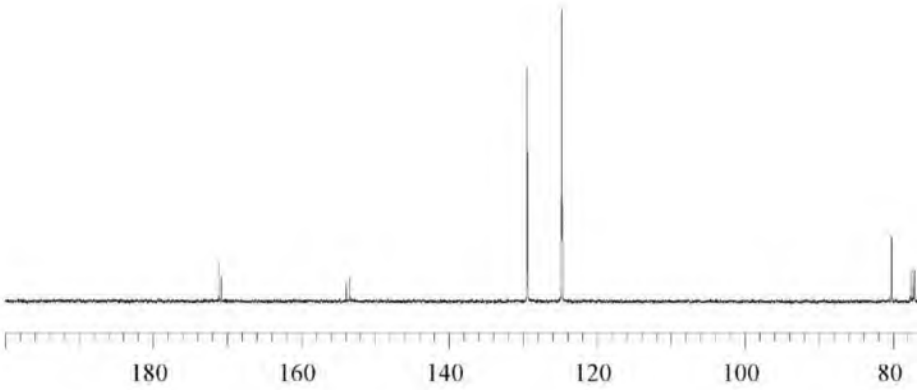
3.45
^{1}H NMR (500 MHz, $CDCl_3$)



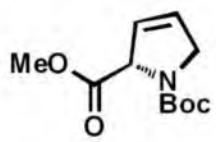

0
1
2
3
ppm



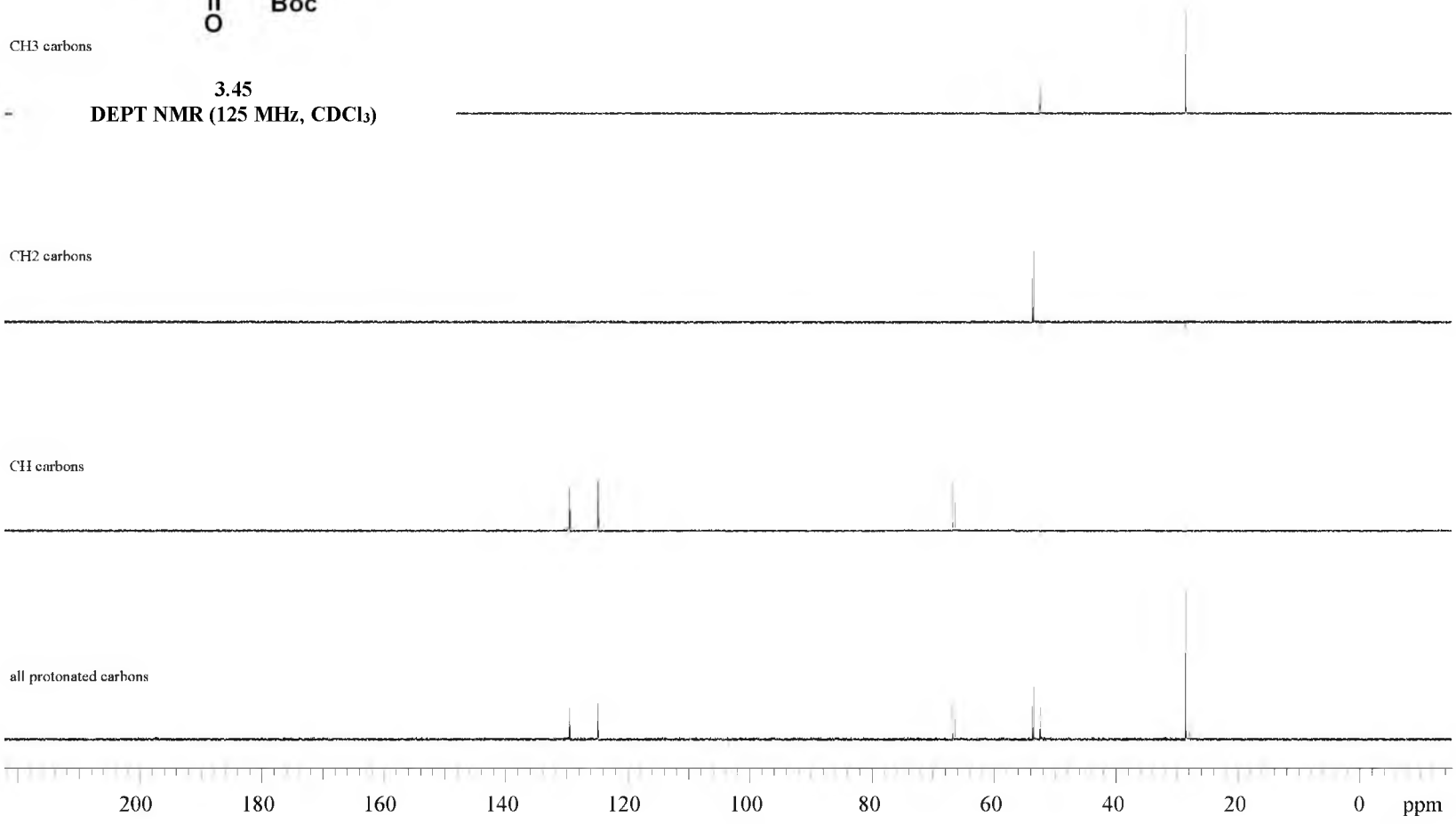
3.45
^{13}C NMR (125 MHz, $CDCl_3$)

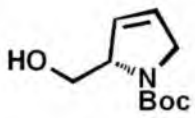



ppm
0
20
40
60

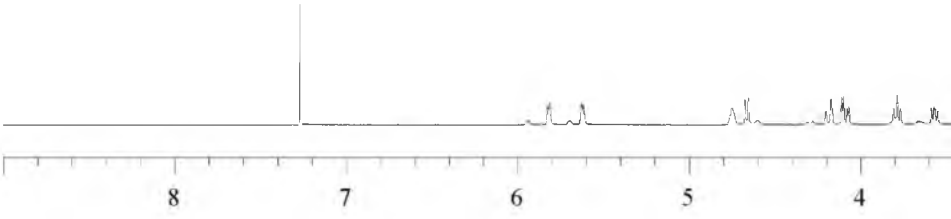


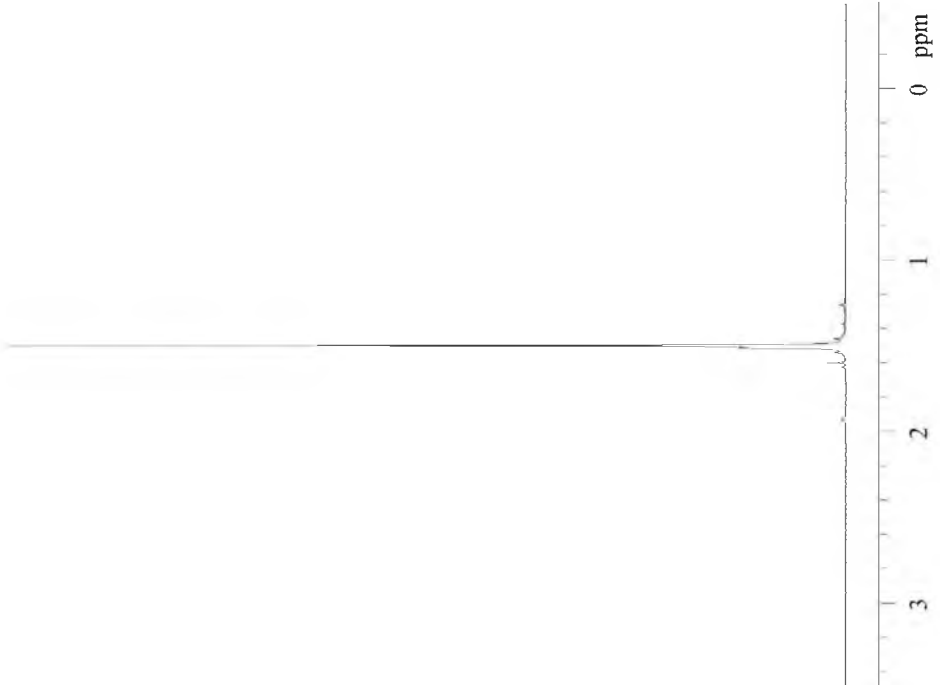
3.45
DEPT NMR (125 MHz, $CDCl_3$)

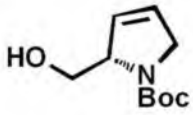




3.39
^{1}H NMR (500 MHz, $CDCl_3$)

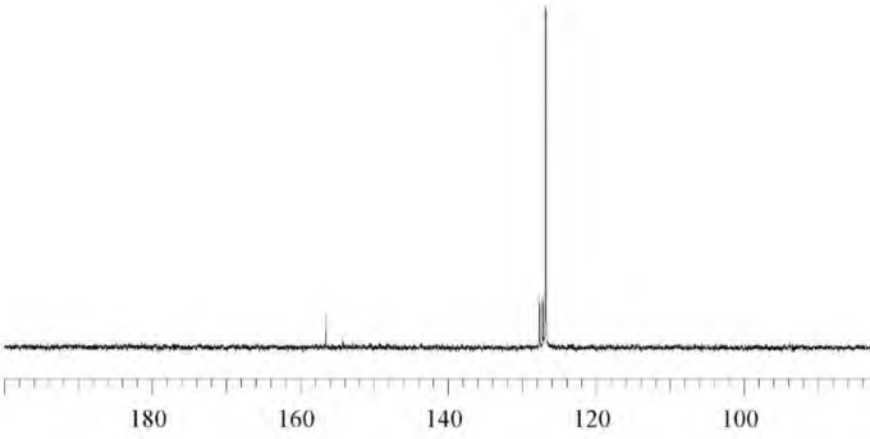


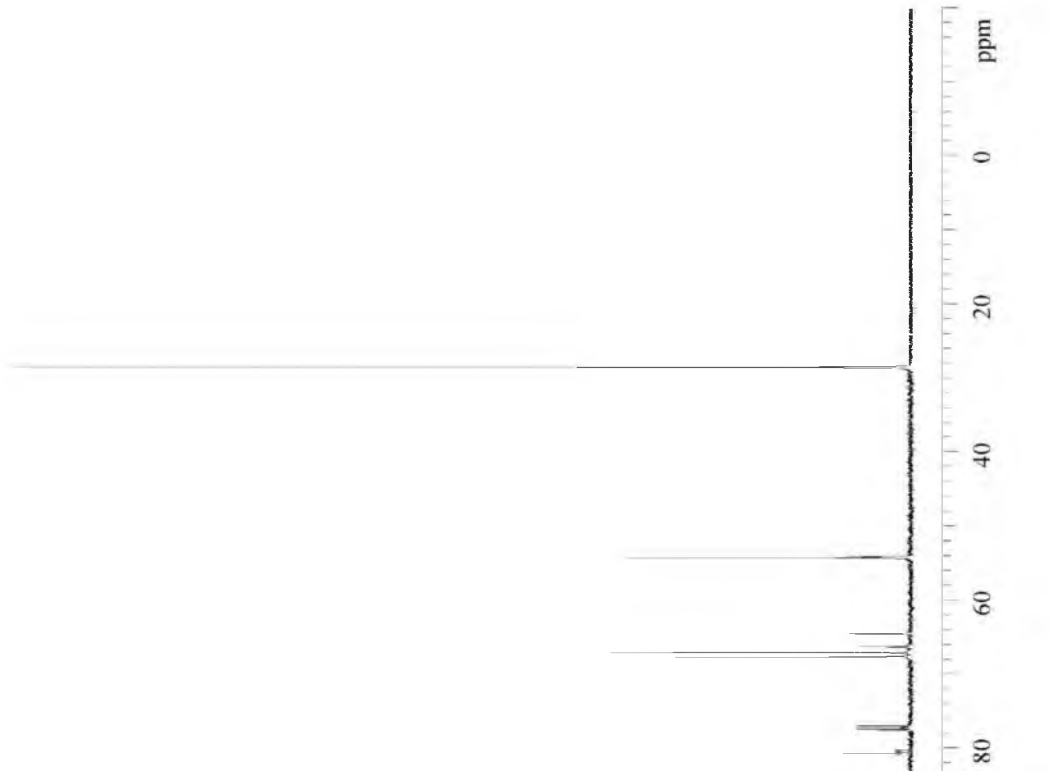

0
1
2
3
ppm



3.39

^{13}C NMR (125 MHz, $CDCl_3$)




ppm
0
20
40
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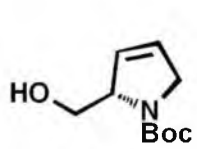
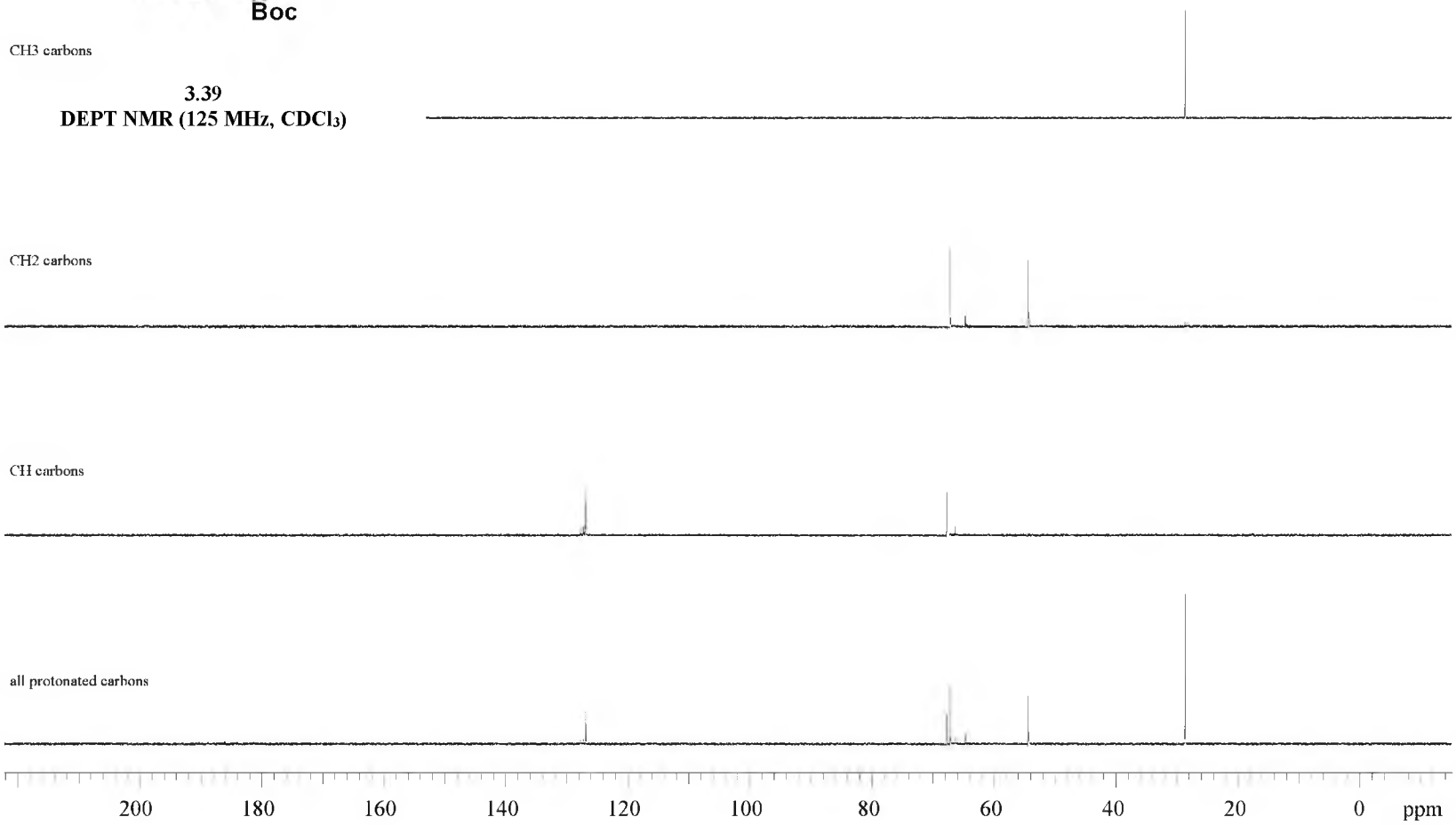
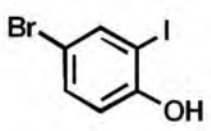
80

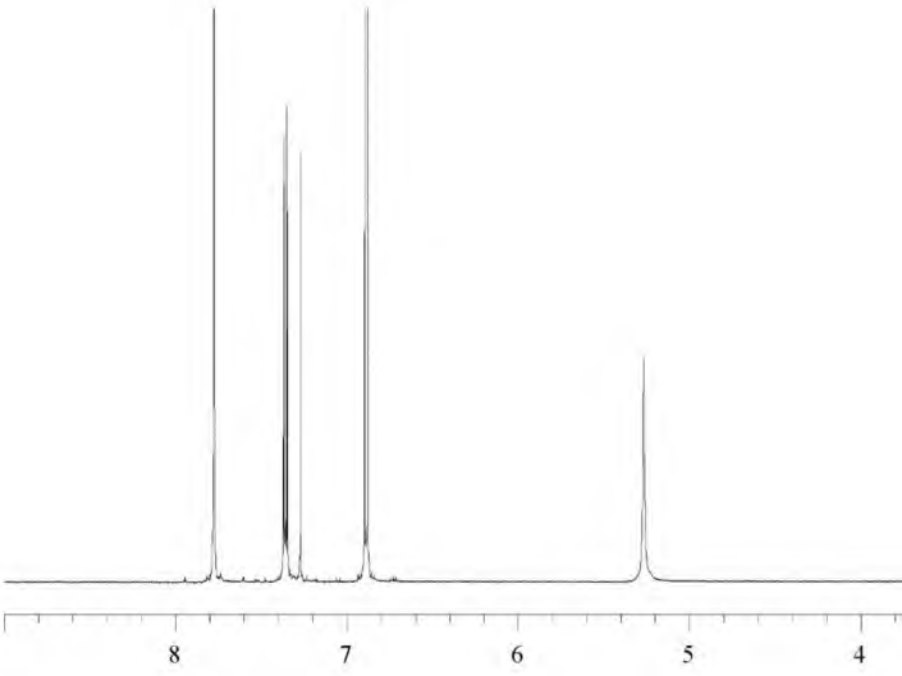


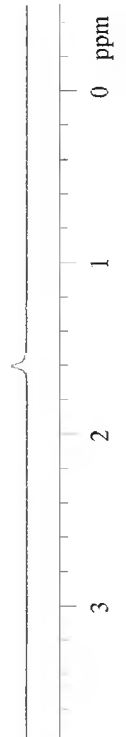
3.39
DEPT NMR (125 MHz, $CDCl_3$)

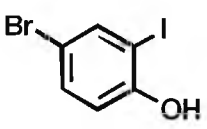




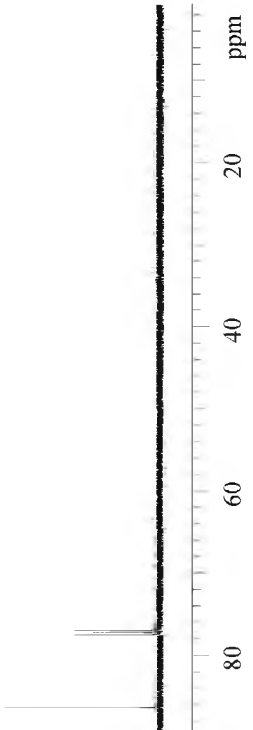
3.46
^{1}H NMR (500 MHz, $CDCl_3$)




ppm
0
1
2
3



3.46
^{13}C NMR (125 MHz, $CDCl_3$)


ppm
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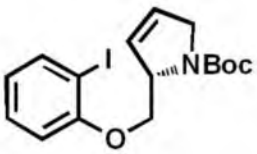
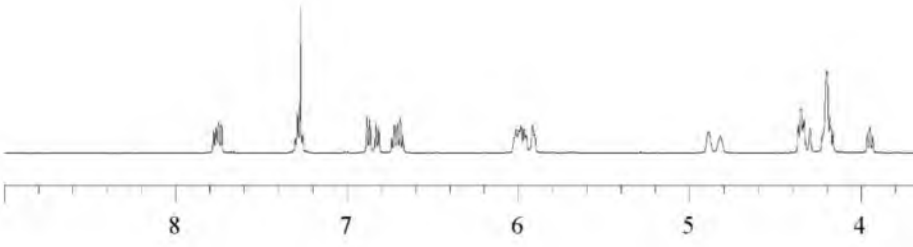
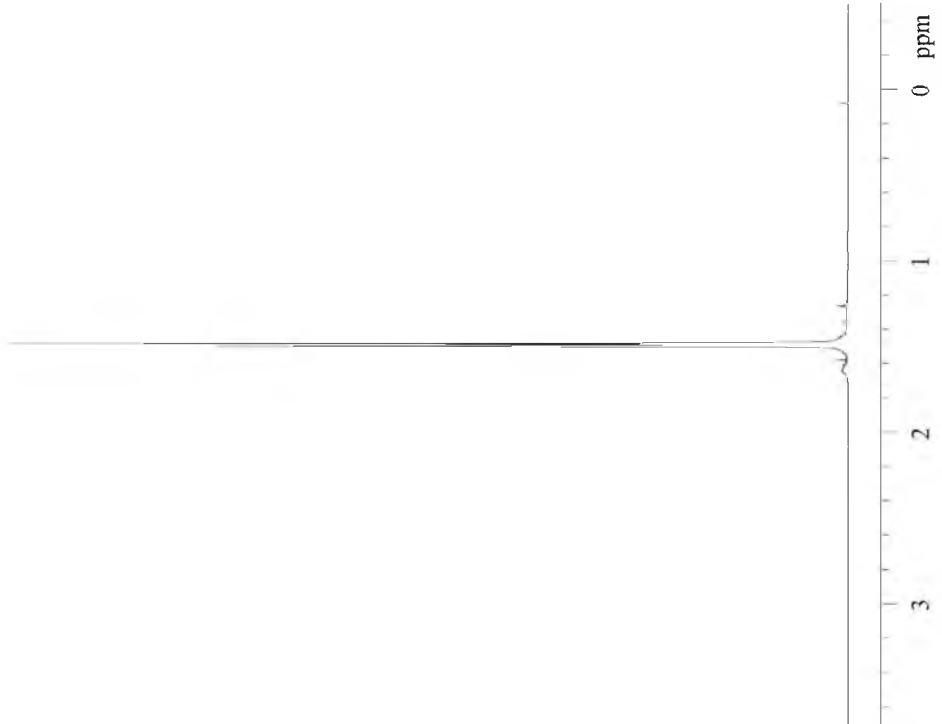
80



3.47
^{1}H NMR (500 MHz, $CDCl_3$)




0
1
2
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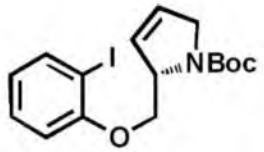
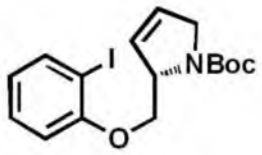
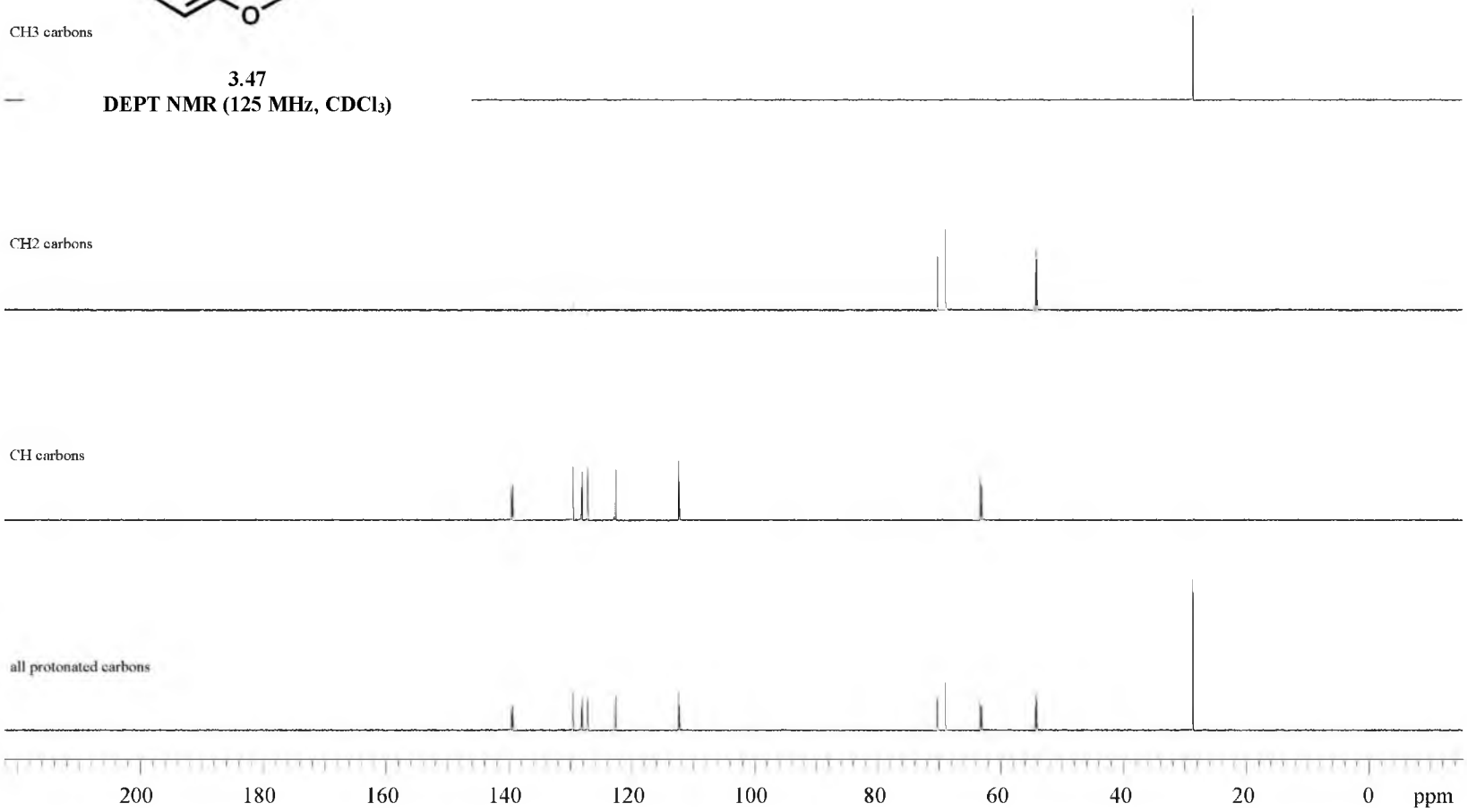
ppm

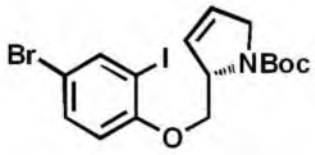


3.47
^{13}C NMR (125 MHz, $CDCl_3$)

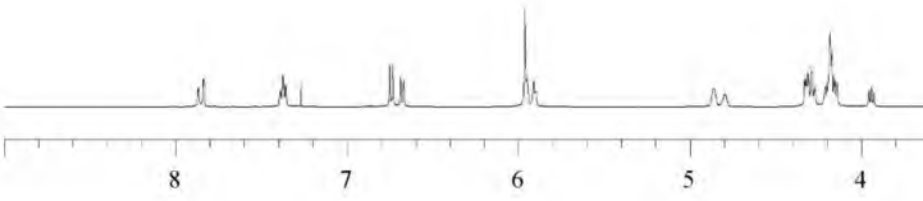


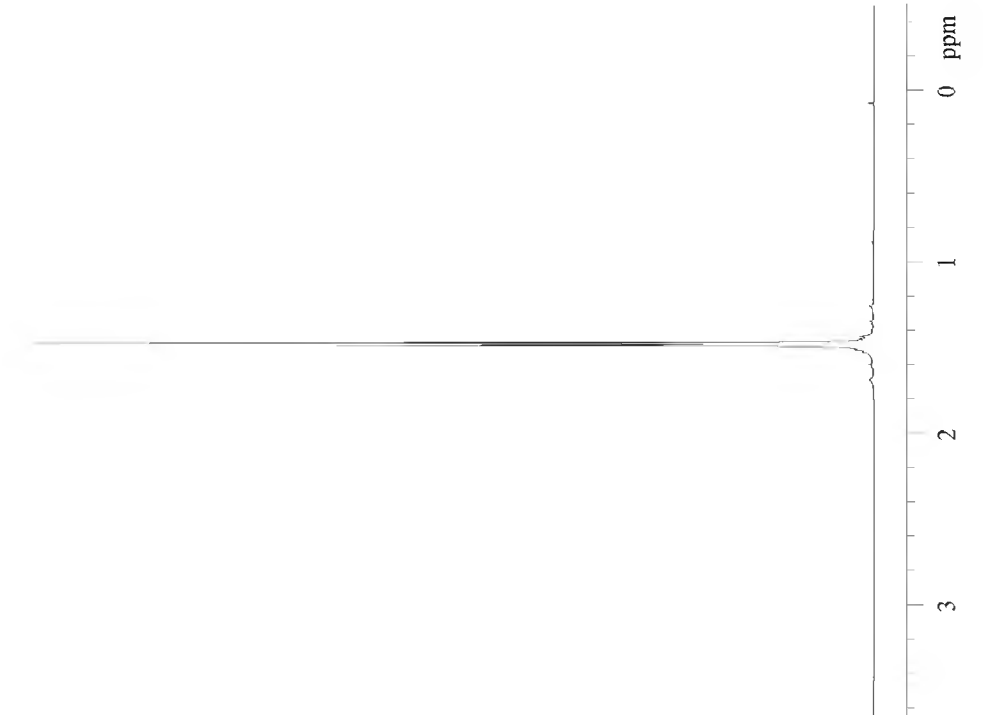
3.47
DEPT NMR (125 MHz, $CDCl_3$)

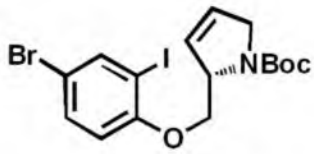




3.48
^{1}H NMR (500 MHz, $CDCl_3$)

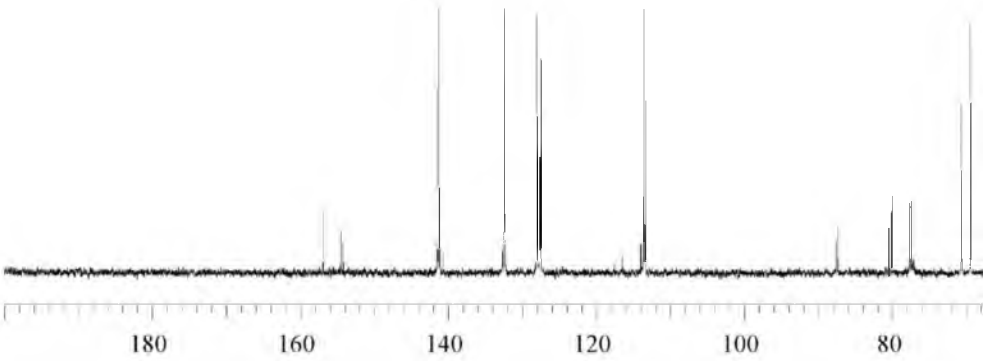



ppm
0
1
2
3

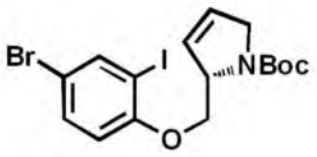


3.48

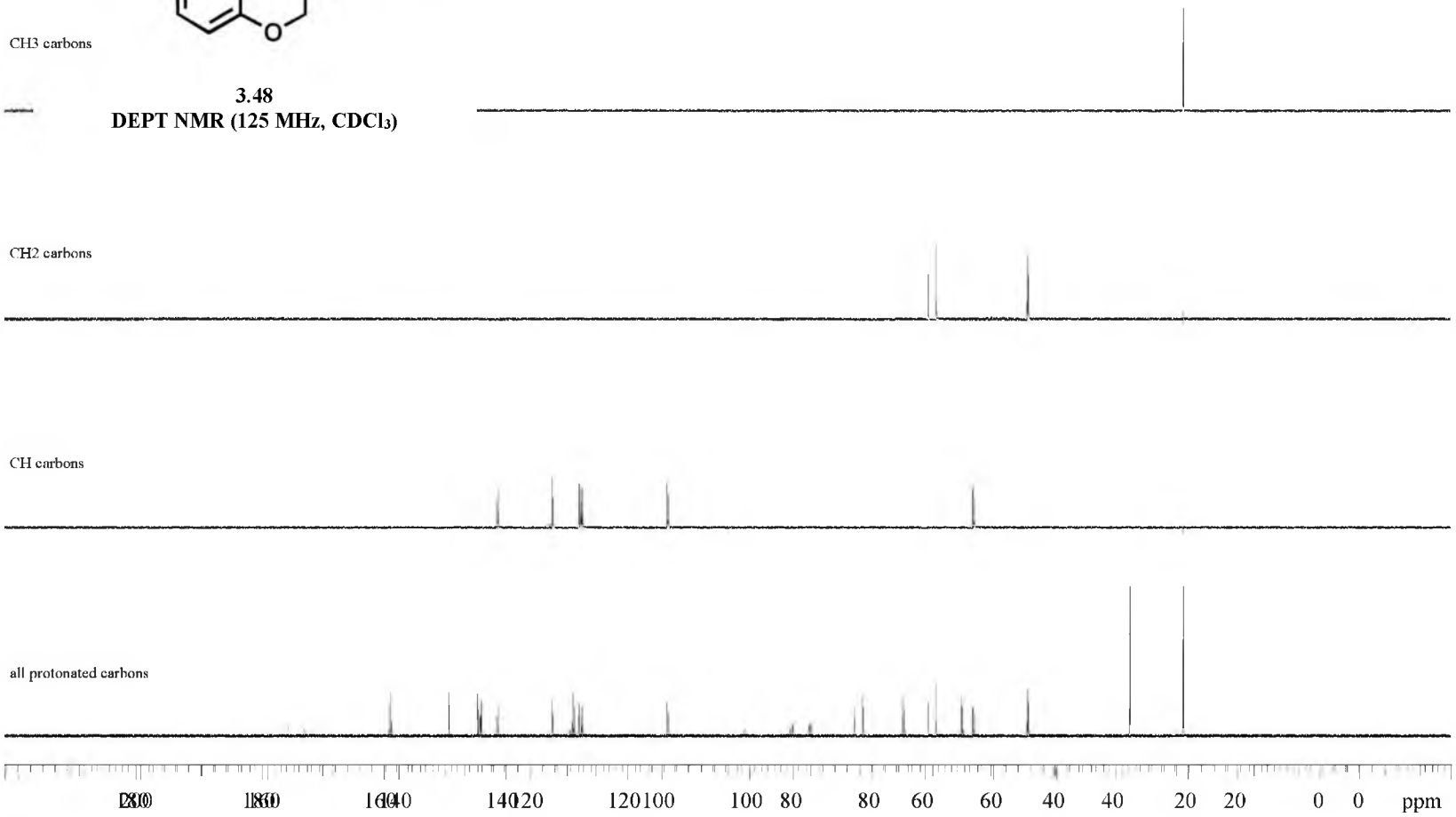
^{13}C NMR (125 MHz, $CDCl_3$)

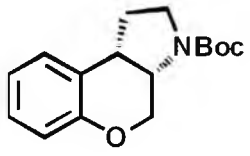



ppm
0
20
40
60

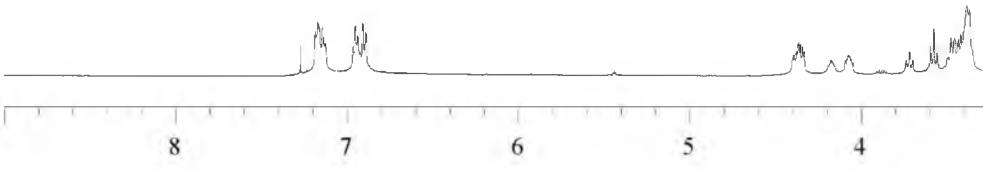


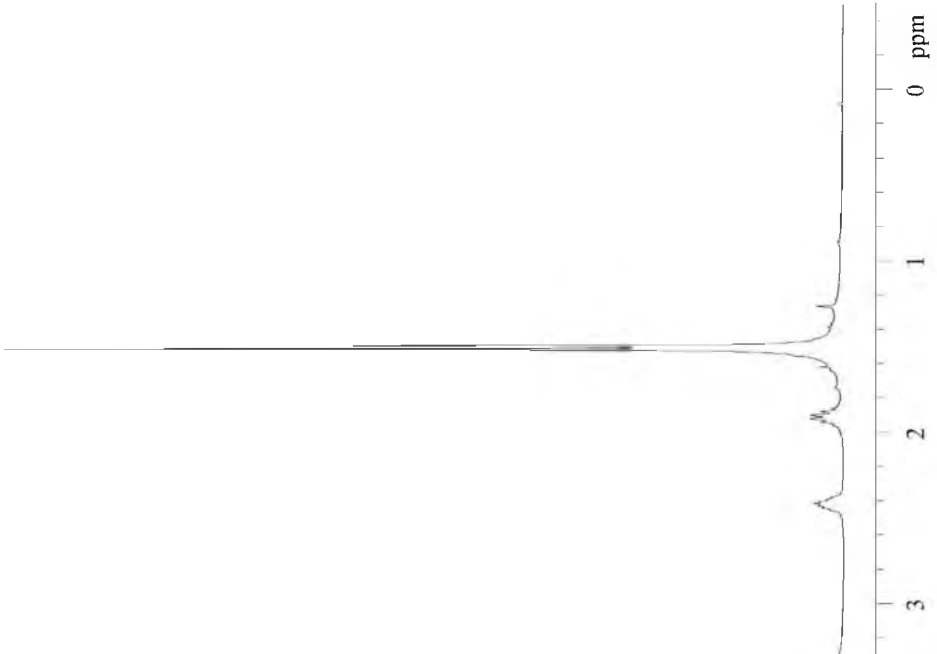
3.48
DEPT NMR (125 MHz, $CDCl_3$)

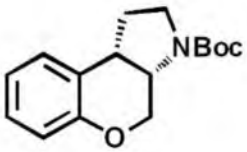




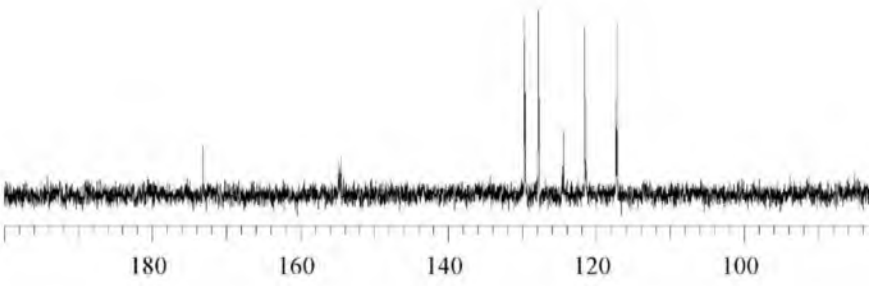
3.49
^{1}H NMR (500 MHz, $CDCl_3$)



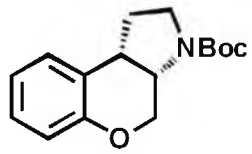

0
ppm
1
2
3



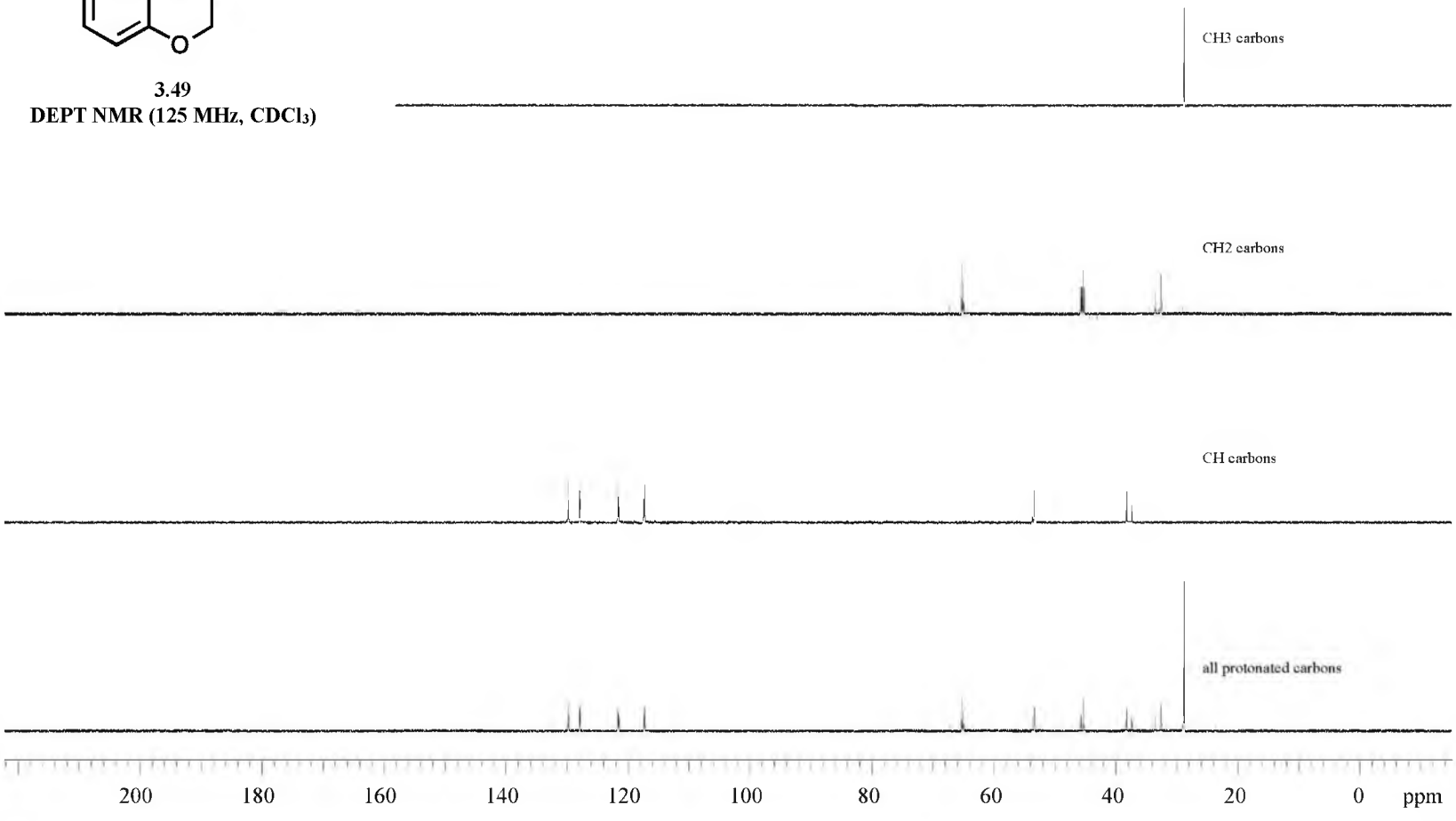
3.49
^{13}C NMR (125 MHz, $CDCl_3$)

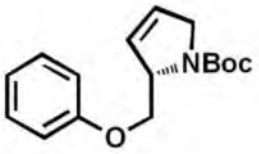



ppm
0
20
40
60
80

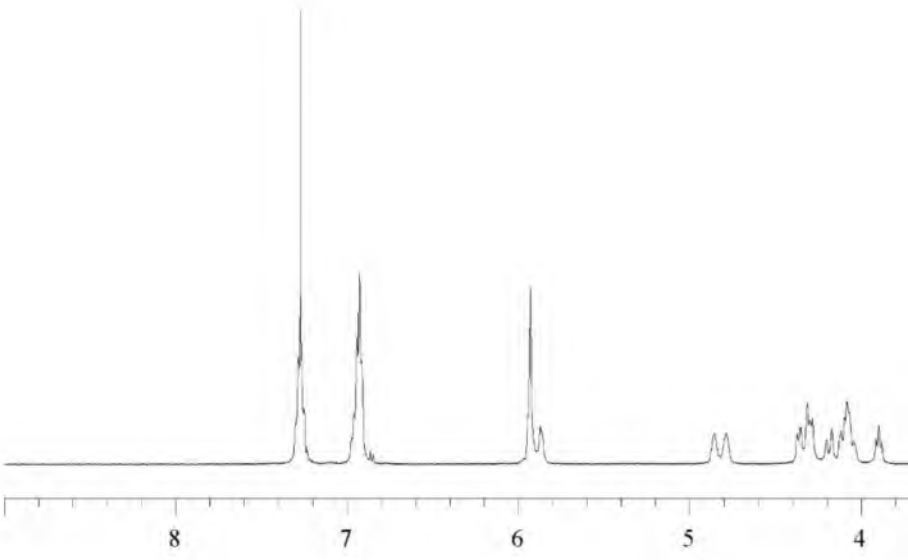


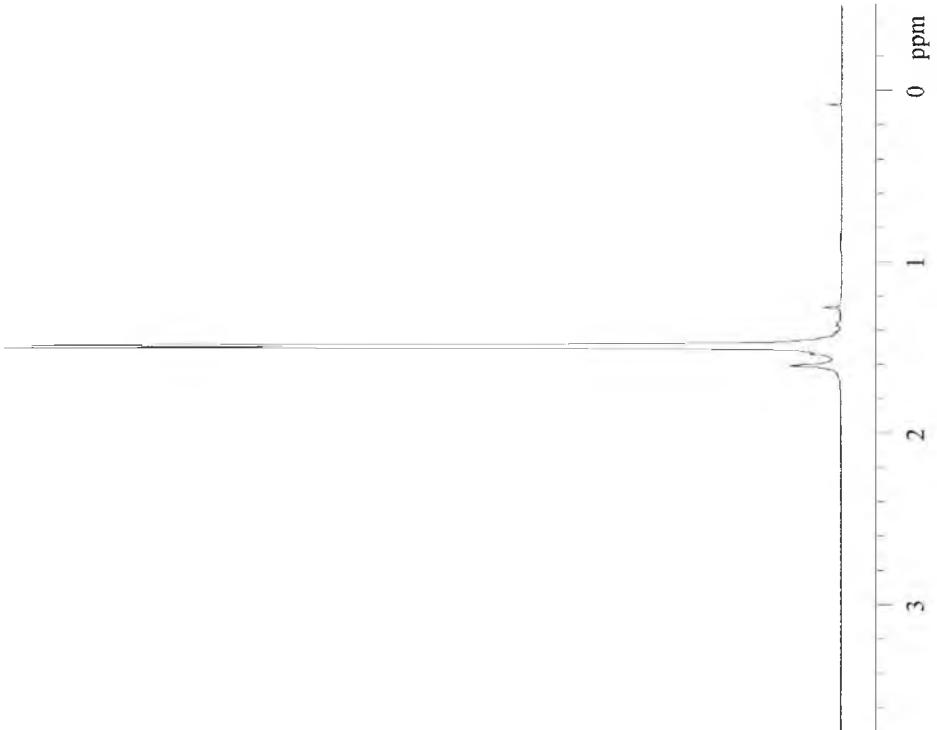
3.49
DEPT NMR (125 MHz, $CDCl_3$)

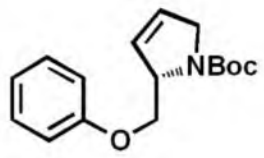




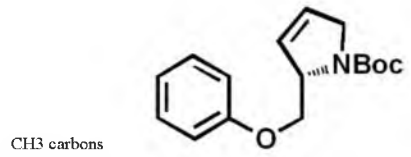
3.50
^{1}H NMR (500 MHz, $CDCl_3$)




0
1
2
3
ppm

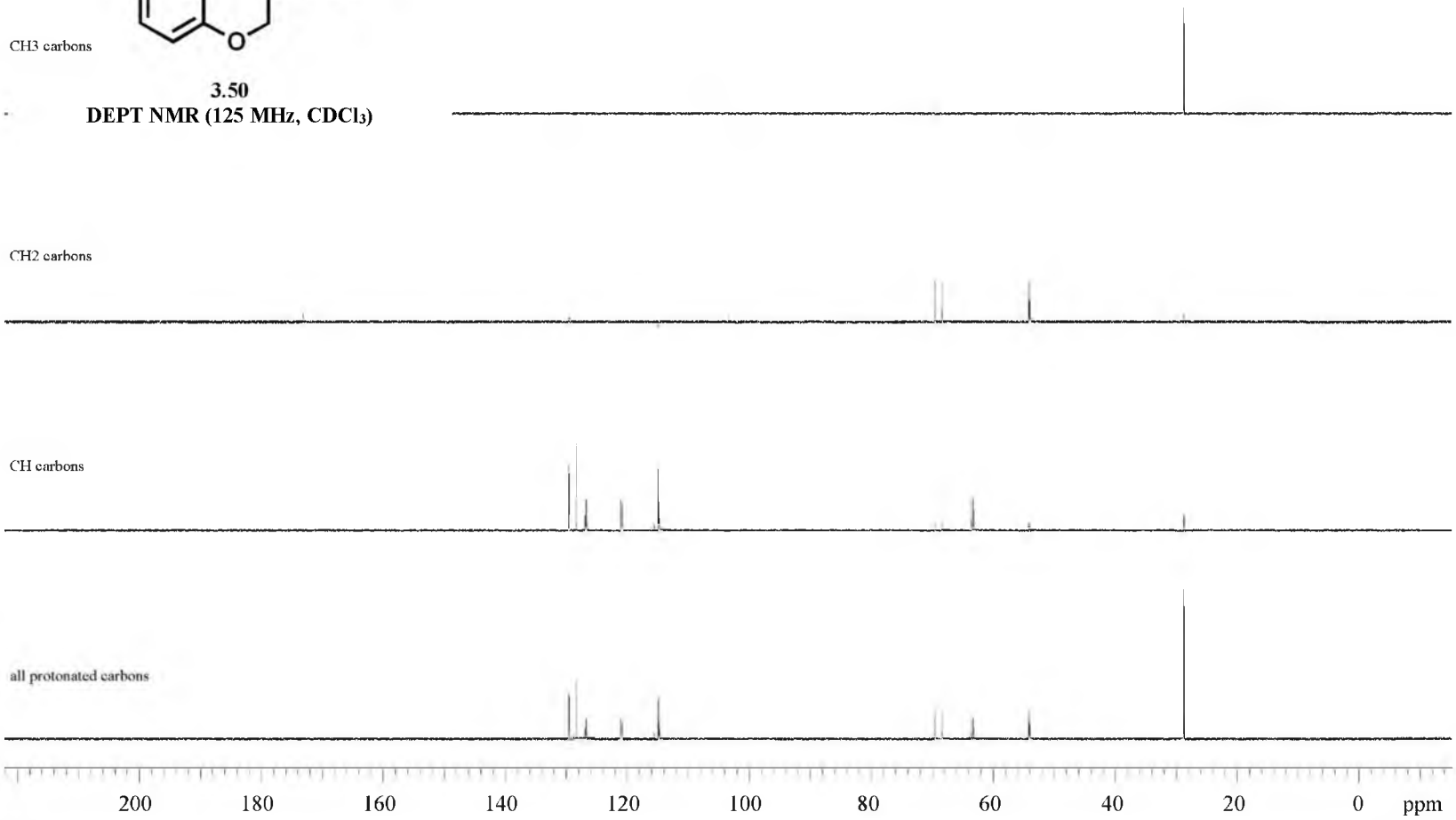


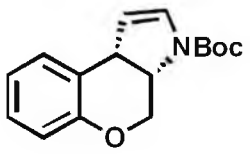
3.50
^{13}C NMR (125 MHz, $CDCl_3$)



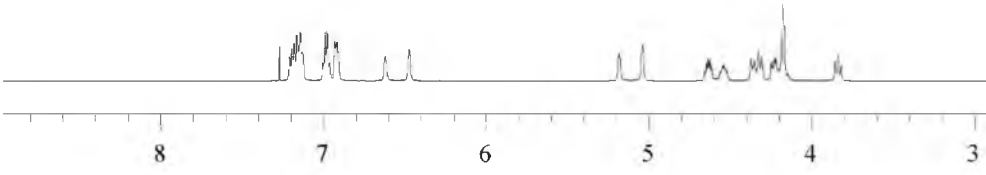
3.50

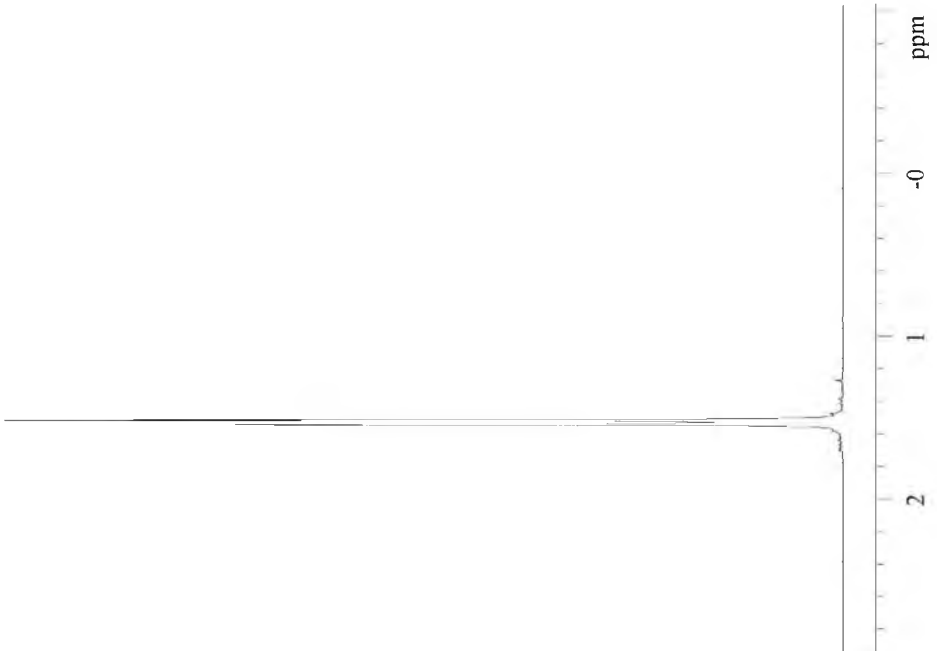
DEPT NMR (125 MHz, $CDCl_3$)

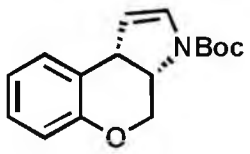




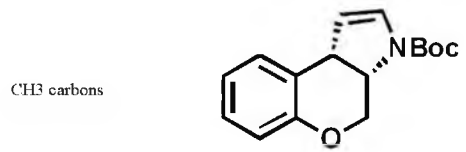
3.51
^{1}H NMR (500 MHz, $CDCl_3$)



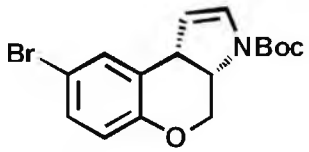

ppm
-0
1
2



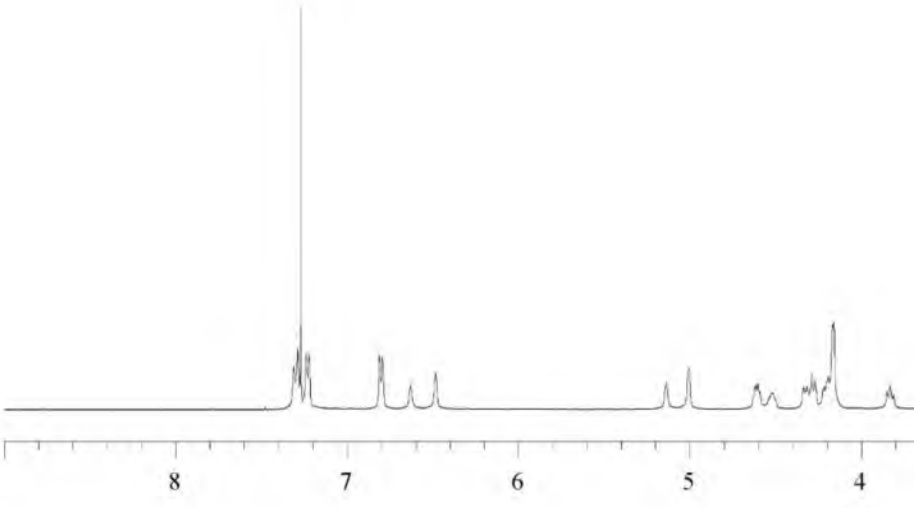
3.51
^{13}C NMR (125 MHz, $CDCl_3$)

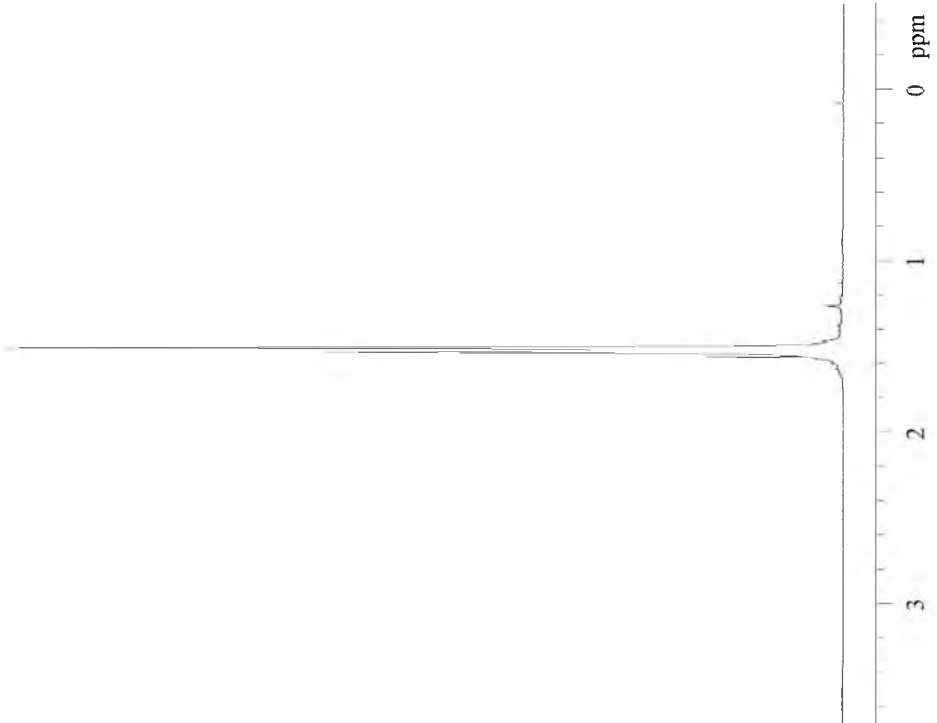


3.51
DEPT NMR (125 MHz, $CDCl_3$)



3.52
^{1}H NMR (500 MHz, $CDCl_3$)

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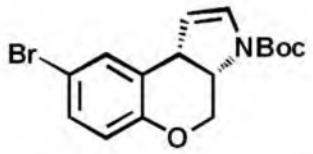
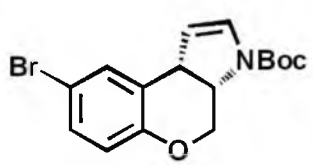
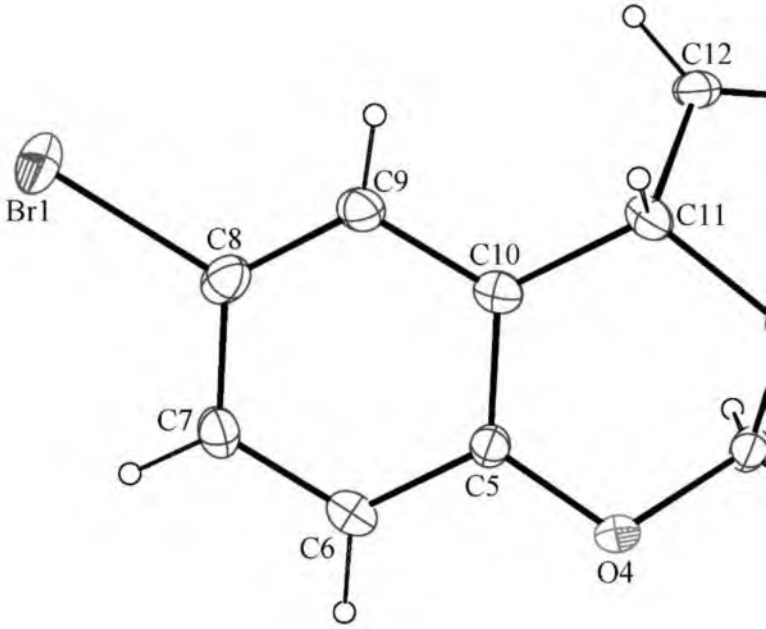
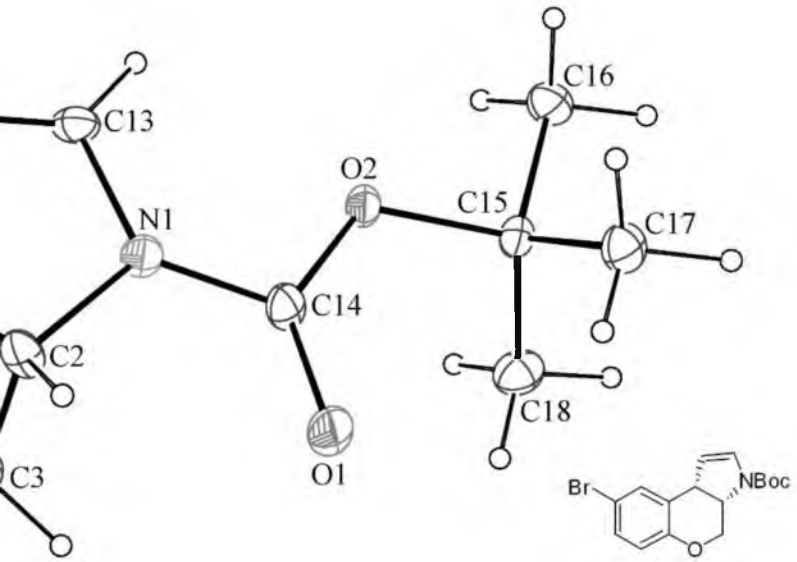


3.52
^{13}C NMR (125 MHz, $CDCl_3$)



3.52
DEPT NMR (125 MHz, $CDCl_3$)


C12
Br1
C9
C11
C8
C10
C7
C5
C6
O4



3.52

Table C.1. Crystal data and structure refinement for **3.52**.

Identification code	gek006
Empirical formula	C16 H18 Br N O3
Formula weight	352.22
Temperature	150(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 7.4043(2) Å □= 90°.
	b = 5.55780(10) Å □= 92.3225(10)°.
	c = 18.9203(6) Å □ = 90°.
Volume	777.96(4) Å^3
Z	2
Density (calculated)	1.504 Mg/m^3
Absorption coefficient	2.651 mm^{-1}
F(000)	360
Crystal size	0.45 x 0.43 x 0.10 mm^3
Theta range for data collection	2.75 to 27.87°.
Index ranges	-9<=h<=9, -7<=k<=6, -24<=l<=24
Reflections collected	3178
Independent reflections	3178 [R(int) = 0.0000]
Completeness to theta = 27.87°	98.8 %
Absorption correction	Multi-scan
Max. and min. transmission	0.7774 and 0.3817
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3178 / 1 / 264
Goodness-of-fit on F^2	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.0933
R indices (all data)	R1 = 0.0432, wR2 = 0.0958
Absolute structure parameter	0.015(11)
Extinction coefficient	0.017(3)
Largest diff. peak and hole	1.061 and -0.854 e.Å^{-3} about 0.805 Å from Br atom

Table C.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

	x	y	z	U(eq)
Br(1)	7989(1)	9890(1)	10005(1)	43(1)
O(1)	5744(3)	-1461(5)	13607(2)	29(1)
O(2)	2737(3)	-501(5)	13496(1)	19(1)
O(4)	9048(3)	4155(5)	12690(1)	23(1)
N(1)	4651(4)	982(6)	12730(2)	21(1)
C(2)	6439(4)	1563(7)	12463(2)	20(1)
C(3)	7419(5)	3248(7)	12980(2)	22(1)
C(5)	8749(4)	5424(6)	12075(2)	18(1)
C(6)	9983(5)	7211(7)	11917(2)	23(1)
C(7)	9773(5)	8546(7)	11308(2)	24(1)
C(8)	8295(5)	8045(7)	10854(2)	26(1)
C(9)	7076(5)	6280(7)	10994(2)	23(1)
C(10)	7271(4)	4919(8)	11612(2)	19(1)
C(11)	5983(5)	2896(7)	11756(2)	21(1)
C(12)	4024(5)	3595(8)	11845(2)	24(1)
C(13)	3330(4)	2396(7)	12375(2)	21(1)
C(14)	4465(4)	-443(7)	13312(2)	20(1)
C(15)	2205(4)	-1892(6)	14120(2)	18(1)
C(16)	202(5)	-1345(8)	14141(2)	24(1)
C(17)	2524(5)	-4540(6)	14002(2)	24(1)
C(18)	3214(6)	-969(8)	14782(2)	26(1)

Table C.3. Bond lengths [Å] and angles [°] for **3.52**.

Br(1)-C(8)	1.912(4)
O(1)-C(14)	1.219(4)
O(2)-C(14)	1.340(4)
O(2)-C(15)	1.478(4)
O(4)-C(5)	1.370(4)
O(4)-C(3)	1.437(4)
N(1)-C(14)	1.367(5)
N(1)-C(13)	1.405(5)
N(1)-C(2)	1.472(4)
C(2)-C(3)	1.518(5)
C(2)-C(11)	1.555(5)
C(2)-H(2)	1.01(5)
C(3)-H(3B)	0.92(5)
C(3)-H(3A)	0.95(5)
C(5)-C(6)	1.390(5)
C(5)-C(10)	1.402(4)
C(6)-C(7)	1.374(5)
C(6)-H(6)	0.95(5)
C(7)-C(8)	1.392(5)
C(7)-H(7)	0.90(5)
C(8)-C(9)	1.366(6)
C(9)-C(10)	1.395(5)
C(9)-H(9)	0.85(6)
C(10)-C(11)	1.506(5)
C(11)-C(12)	1.517(5)
C(11)-H(11)	1.05(5)
C(12)-C(13)	1.325(5)
C(12)-H(12)	0.90(5)
C(13)-H(13)	1.01(4)
C(15)-C(17)	1.508(5)
C(15)-C(16)	1.516(5)
C(15)-C(18)	1.521(5)
C(16)-H(16A)	0.97(5)
C(16)-H(16C)	0.97(6)

Table C.3. Continued

C(16)-H(16B)	0.94(5)
C(17)-H(17C)	1.00(4)
C(17)-H(17A)	0.89(4)
C(17)-H(17B)	0.89(4)
C(18)-H(18B)	0.99(6)
C(18)-H(18C)	1.02(6)
C(18)-H(18A)	0.90(6)
C(14)-O(2)-C(15)	120.6(3)
C(5)-O(4)-C(3)	113.3(2)
C(14)-N(1)-C(13)	128.2(3)
C(14)-N(1)-C(2)	121.7(3)
C(13)-N(1)-C(2)	109.3(3)
N(1)-C(2)-C(3)	109.0(3)
N(1)-C(2)-C(11)	103.5(3)
C(3)-C(2)-C(11)	110.0(3)
N(1)-C(2)-H(2)	107(2)
C(3)-C(2)-H(2)	115(2)
C(11)-C(2)-H(2)	112(2)
O(4)-C(3)-C(2)	110.8(3)
O(4)-C(3)-H(3B)	108(3)
C(2)-C(3)-H(3B)	113(2)
O(4)-C(3)-H(3A)	105(3)
C(2)-C(3)-H(3A)	111(3)
H(3B)-C(3)-H(3A)	108(4)
O(4)-C(5)-C(6)	117.7(3)
O(4)-C(5)-C(10)	121.5(3)
C(6)-C(5)-C(10)	120.8(3)
C(7)-C(6)-C(5)	120.9(3)
C(7)-C(6)-H(6)	116(3)
C(5)-C(6)-H(6)	123(3)
C(6)-C(7)-C(8)	118.0(4)
C(6)-C(7)-H(7)	122(2)
C(8)-C(7)-H(7)	120(2)
C(9)-C(8)-C(7)	122.2(3)

Table C.3. Continued

C(9)-C(8)-Br(1)	119.4(3)
C(7)-C(8)-Br(1)	118.3(3)
C(8)-C(9)-C(10)	120.3(3)
C(8)-C(9)-H(9)	127(4)
C(10)-C(9)-H(9)	112(4)
C(9)-C(10)-C(5)	117.8(3)
C(9)-C(10)-C(11)	120.7(3)
C(5)-C(10)-C(11)	121.4(3)
C(10)-C(11)-C(12)	116.4(3)
C(10)-C(11)-C(2)	113.2(3)
C(12)-C(11)-C(2)	101.6(3)
C(10)-C(11)-H(11)	105(3)
C(12)-C(11)-H(11)	111(3)
C(2)-C(11)-H(11)	110(3)
C(13)-C(12)-C(11)	110.9(3)
C(13)-C(12)-H(12)	126(3)
C(11)-C(12)-H(12)	123(3)
C(12)-C(13)-N(1)	111.1(3)
C(12)-C(13)-H(13)	130(3)
N(1)-C(13)-H(13)	118(3)
O(1)-C(14)-O(2)	126.9(3)
O(1)-C(14)-N(1)	122.4(3)
O(2)-C(14)-N(1)	110.6(3)
O(2)-C(15)-C(17)	110.1(3)
O(2)-C(15)-C(16)	102.0(3)
C(17)-C(15)-C(16)	111.0(3)
O(2)-C(15)-C(18)	110.1(3)
C(17)-C(15)-C(18)	112.1(3)
C(16)-C(15)-C(18)	111.0(3)
C(15)-C(16)-H(16A)	108(3)
C(15)-C(16)-H(16C)	109(3)
H(16A)-C(16)-H(16C)	110(4)
C(15)-C(16)-H(16B)	111(3)
H(16A)-C(16)-H(16B)	106(4)

Table C.3. Continued

H(16C)-C(16)-H(16B)	114(4)
C(15)-C(17)-H(17C)	111(3)
C(15)-C(17)-H(17A)	110(4)
H(17C)-C(17)-H(17A)	106(4)
C(15)-C(17)-H(17B)	105(4)
H(17C)-C(17)-H(17B)	109(4)
H(17A)-C(17)-H(17B)	116(4)
C(15)-C(18)-H(18B)	110(3)
C(15)-C(18)-H(18C)	114(3)
H(18B)-C(18)-H(18C)	97(4)
C(15)-C(18)-H(18A)	117(4)
H(18B)-C(18)-H(18A)	110(5)
H(18C)-C(18)-H(18A)	108(5)

Table C.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **3.52**.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	41(1)	59(1)	28(1)	21(1)	3(1)	-3(1)
O(1)	19(1)	25(1)	44(2)	15(1)	3(1)	8(1)
O(2)	15(1)	20(1)	23(1)	8(1)	3(1)	1(1)
O(4)	16(1)	26(2)	27(1)	7(1)	-4(1)	1(1)
N(1)	14(1)	22(2)	26(2)	6(1)	3(1)	5(1)
C(2)	15(1)	17(2)	29(2)	-1(1)	7(1)	3(1)
C(3)	21(2)	24(2)	21(2)	8(1)	3(1)	2(2)
C(5)	16(1)	20(2)	19(1)	3(1)	3(1)	3(1)
C(6)	18(2)	23(2)	27(2)	-5(1)	2(1)	-2(1)
C(7)	22(2)	24(2)	25(2)	3(1)	6(1)	-2(2)
C(8)	23(2)	33(2)	21(2)	5(2)	3(1)	7(2)
C(9)	18(2)	33(2)	19(2)	0(1)	2(1)	-1(2)
C(10)	16(1)	22(2)	19(1)	-5(2)	2(1)	2(2)
C(11)	18(2)	28(2)	17(2)	-5(1)	3(1)	-5(1)
C(12)	17(2)	35(2)	19(2)	3(2)	-3(1)	-2(2)
C(13)	14(1)	28(2)	20(2)	0(1)	-1(1)	2(1)
C(14)	19(1)	14(2)	28(2)	4(1)	3(1)	2(1)
C(15)	19(2)	18(2)	17(2)	4(1)	2(1)	-1(1)
C(16)	17(2)	29(2)	25(2)	2(2)	2(1)	-1(2)
C(17)	29(2)	17(2)	26(2)	0(1)	-1(1)	-1(1)
C(18)	30(2)	25(2)	22(2)	-3(1)	-5(2)	1(2)

Table C.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **3.52**.

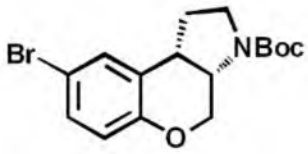
	x	y	z	U(eq)
H(7)	10540(50)	9730(100)	11204(18)	18(8)
H(2)	7080(40)	-10(100)	12383(18)	18(8)
H(3B)	6720(50)	4540(90)	13110(20)	23(10)
H(17C)	2070(50)	-5510(90)	14410(20)	22(10)
H(12)	3420(60)	4640(110)	11550(20)	35(11)
H(17A)	3700(60)	-4830(110)	13990(20)	34(12)
H(17B)	1880(50)	-4900(110)	13610(20)	31(11)
H(11)	6100(60)	1710(90)	11330(20)	31(12)
H(3A)	7800(60)	2440(90)	13400(20)	24(11)
H(6)	10950(70)	7670(90)	12230(30)	33(12)
H(16A)	-260(60)	-2190(90)	14540(20)	27(11)
H(18B)	2640(70)	-1610(100)	15210(30)	39(14)
H(16C)	40(60)	380(110)	14200(20)	28(12)
H(13)	2090(60)	2490(90)	12580(20)	26(11)
H(18C)	2990(70)	810(100)	14880(30)	29(14)
H(9)	6140(90)	5900(120)	10750(30)	70(20)
H(18A)	4410(80)	-1220(110)	14810(30)	54(17)
H(16B)	-420(60)	-1980(90)	13740(30)	27(12)

Table C.6. Torsion angles [°] for **3.52**.

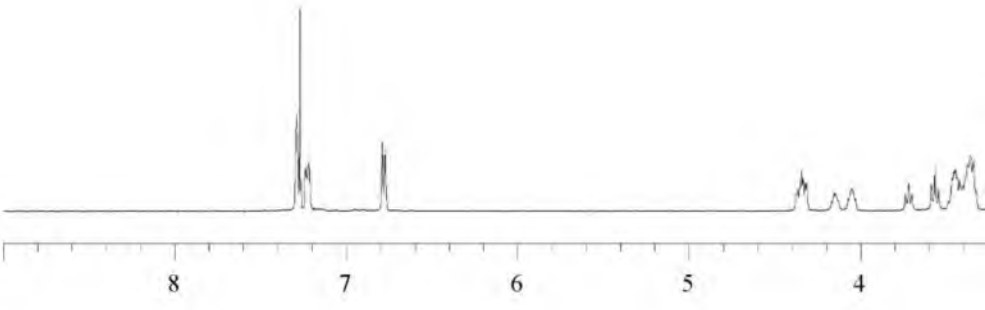
C(14)-N(1)-C(2)-C(3)	-70.3(4)
C(13)-N(1)-C(2)-C(3)	100.4(3)
C(14)-N(1)-C(2)-C(11)	172.6(3)
C(13)-N(1)-C(2)-C(11)	-16.7(4)
C(5)-O(4)-C(3)-C(2)	60.1(4)
N(1)-C(2)-C(3)-O(4)	-171.1(3)
C(11)-C(2)-C(3)-O(4)	-58.3(4)
C(3)-O(4)-C(5)-C(6)	152.0(3)
C(3)-O(4)-C(5)-C(10)	-29.1(4)
O(4)-C(5)-C(6)-C(7)	179.7(3)
C(10)-C(5)-C(6)-C(7)	0.8(5)
C(5)-C(6)-C(7)-C(8)	-0.3(6)
C(6)-C(7)-C(8)-C(9)	-0.4(6)
C(6)-C(7)-C(8)-Br(1)	-180.0(3)
C(7)-C(8)-C(9)-C(10)	0.7(6)
Br(1)-C(8)-C(9)-C(10)	-179.8(3)
C(8)-C(9)-C(10)-C(5)	-0.2(5)
C(8)-C(9)-C(10)-C(11)	-177.2(3)
O(4)-C(5)-C(10)-C(9)	-179.4(3)
C(6)-C(5)-C(10)-C(9)	-0.5(5)
O(4)-C(5)-C(10)-C(11)	-2.3(5)
C(6)-C(5)-C(10)-C(11)	176.5(3)
C(9)-C(10)-C(11)-C(12)	-63.9(4)
C(5)-C(10)-C(11)-C(12)	119.2(4)
C(9)-C(10)-C(11)-C(2)	178.9(3)
C(5)-C(10)-C(11)-C(2)	2.0(5)
N(1)-C(2)-C(11)-C(10)	143.5(3)
C(3)-C(2)-C(11)-C(10)	27.1(4)
N(1)-C(2)-C(11)-C(12)	17.9(4)
C(3)-C(2)-C(11)-C(12)	-98.4(3)
C(10)-C(11)-C(12)-C(13)	-137.9(3)
C(2)-C(11)-C(12)-C(13)	-14.5(4)
C(11)-C(12)-C(13)-N(1)	4.7(5)
C(14)-N(1)-C(13)-C(12)	178.1(4)

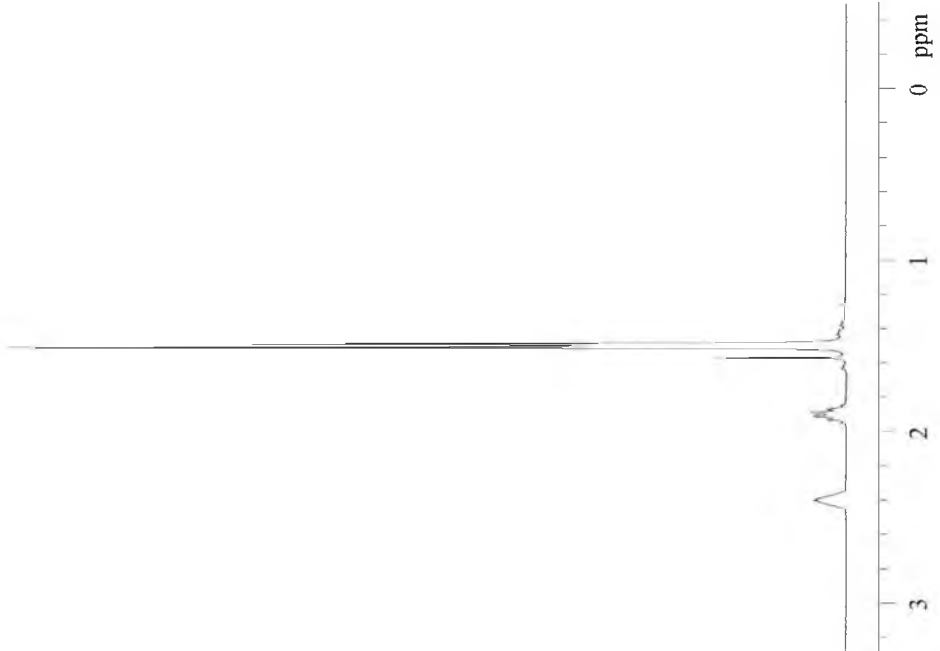
Table C.6 Continued

C(2)-N(1)-C(13)-C(12)	8.1(4)
C(15)-O(2)-C(14)-O(1)	0.4(6)
C(15)-O(2)-C(14)-N(1)	-178.8(3)
C(13)-N(1)-C(14)-O(1)	-174.6(4)
C(2)-N(1)-C(14)-O(1)	-5.8(6)
C(13)-N(1)-C(14)-O(2)	4.6(5)
C(2)-N(1)-C(14)-O(2)	173.4(3)
C(14)-O(2)-C(15)-C(17)	-64.7(4)
C(14)-O(2)-C(15)-C(16)	177.4(3)
C(14)-O(2)-C(15)-C(18)	59.5(4)



3.53
^{1}H NMR (500 MHz, $CDCl_3$)

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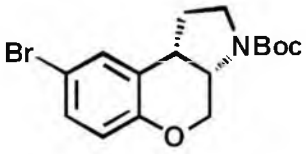
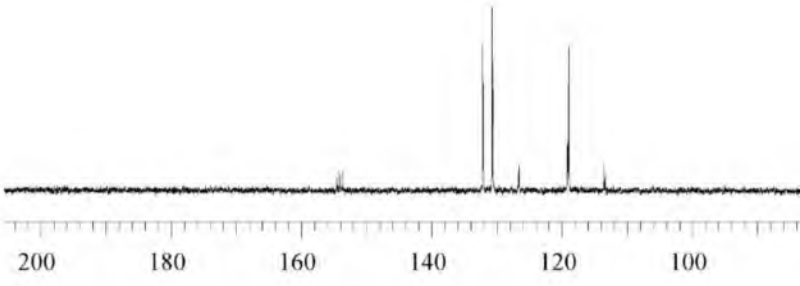
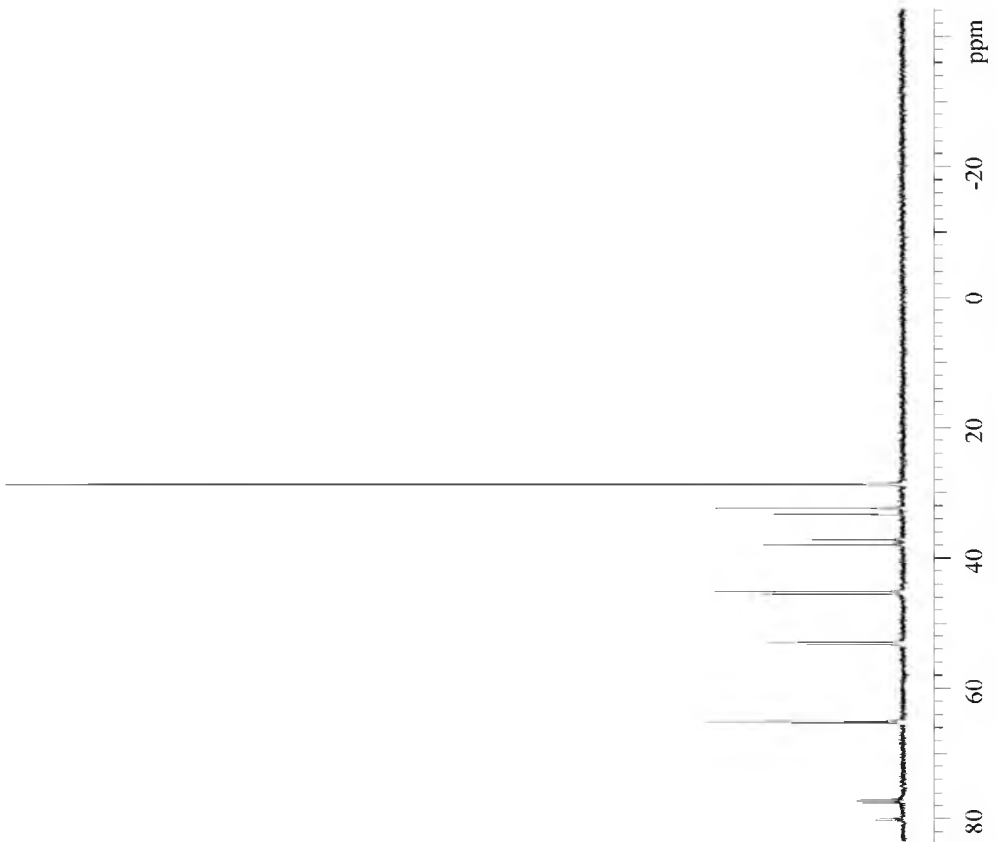


3.53
^{13}C NMR (125 MHz, $CDCl_3$)

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20
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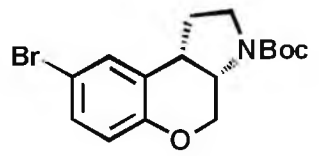
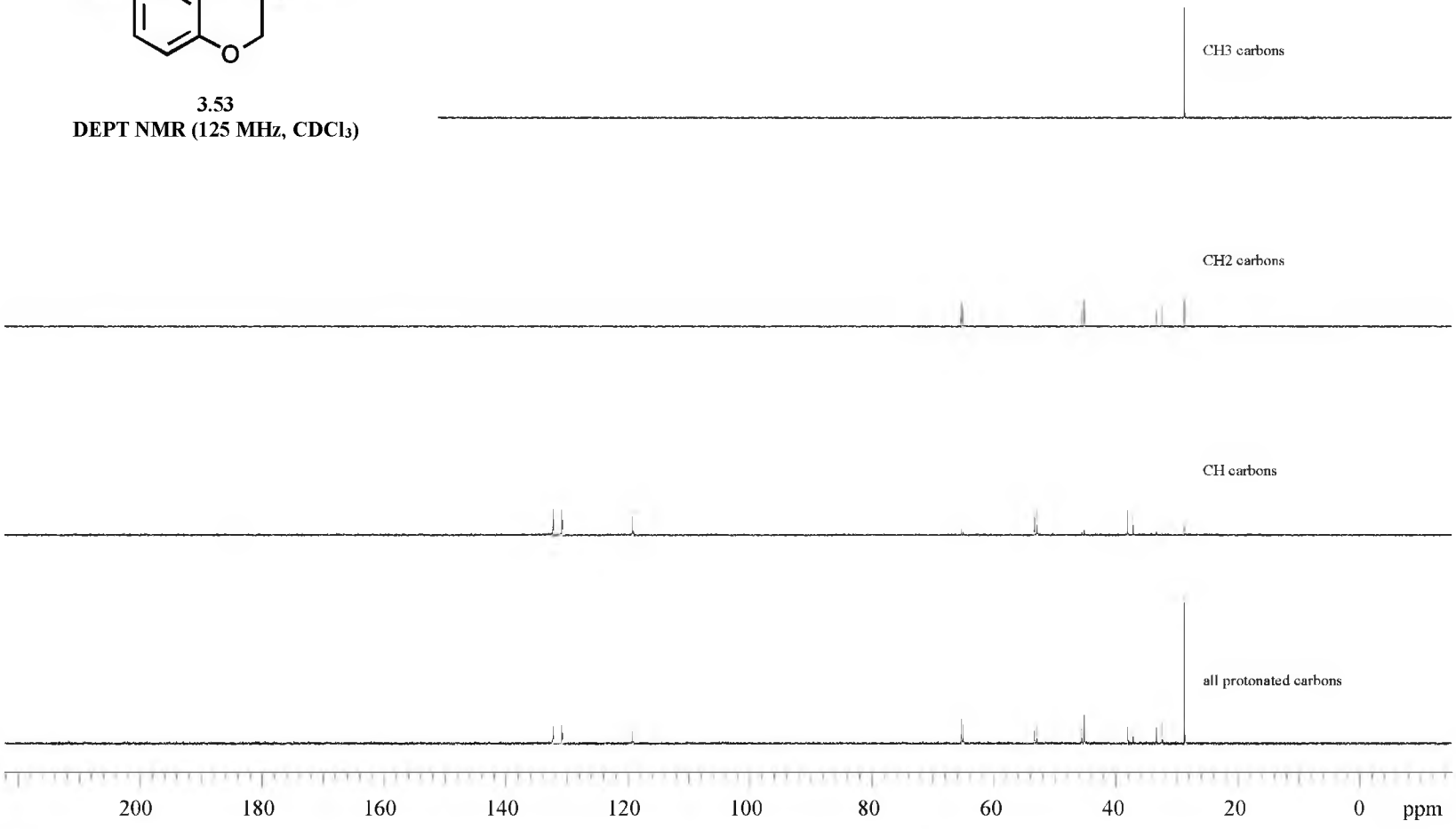
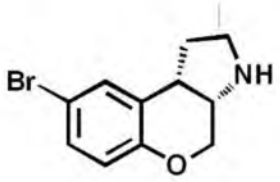
60
80



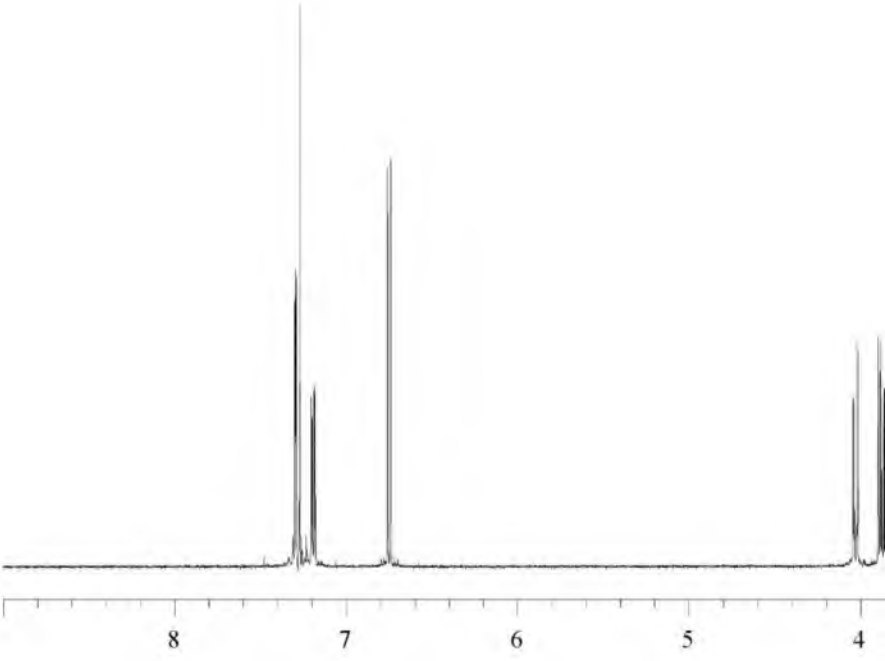
3.53
DEPT NMR (125 MHz, $CDCl_3$)

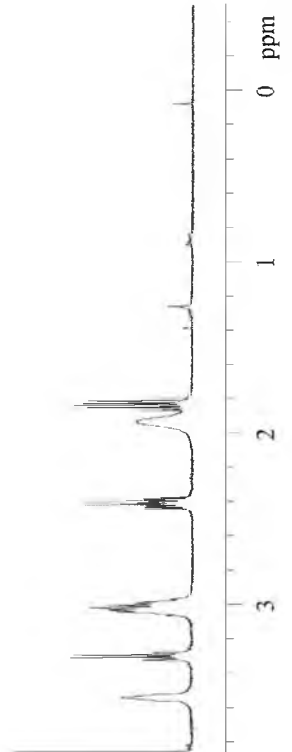


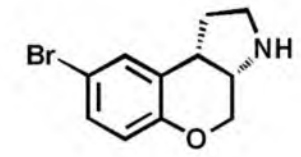


3.54

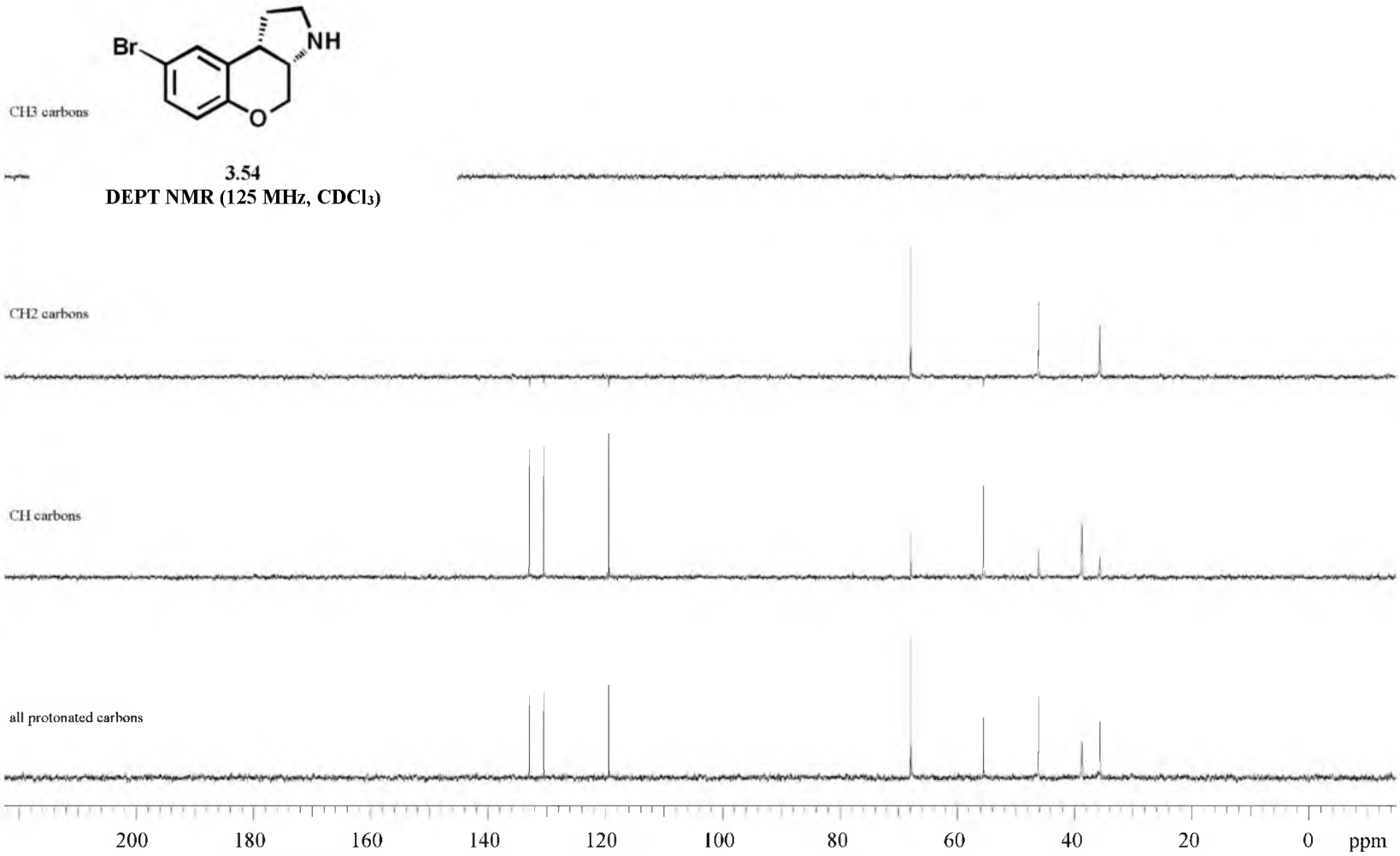
^{1}H NMR (500 MHz, $CDCl_3$)




0
1
2
3
ppm



3.54
^{13}C NMR (125 MHz, $CDCl_3$)



3.54
DEPT NMR (125 MHz, $CDCl_3$)